BRITISH MEDICAL JOURNAL

LONDON SATURDAY JANUARY 2 1960

CLINICAL AND METABOLIC STUDIES IN THYROID DISEASE*

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I have chosen for these two lectures a title which will permit me to cover a very wide field, but which compels me, therefore, to be selective in my approach, and I should like first of all to explain what directed my choice of the topics on which I intend to speak. My interest in thyroid disease was first stimulated soon after I qualified, and since then I have seen and taken part in a steady advance in the diagnosis and treatment of thyroid dysfunction. The direction of my investigations has on several occasions been decided by events in my own particular career, and I hope I may be allowed the pleasure of a few reminiscences which will, I think, make clearer to you the shape of the lectures I am privileged to give to the College.

An important influence on my career was a period spent as an experimental pharmacologist, since this taught me to look statistically at medical problems. Though it is nearly thirty years ago, Professor A. J. Clark, of Edinburgh, was even at that time emphasizing the great variability of biological material, and in particular the variation which the individual animal may show in its response to drugs. He was a pioneer in demonstrating that statistical methods were necessary to deal with this phenomenon, and he and his successor, Professor J. H. Gaddum, extended the scope of these techniques and applied them to human pharmacology.

But my interests were not primarily in the laboratory, and I was soon fortunate enough to obtain an appointment to the Department of Clinical Research at University College Hospital, where I worked under Sir Thomas Lewis. At that time Lewis was formulating his ideas on clinical science. He thought it most profitable to study disease directly under controlled conditions, and to apply in the wards techniques devised by physiologists for the study of normal physiological processes. Though he thought mainly in terms of cardiovascular disease, he would, I am sure, have recognized in some of the studies I shall report the proper tradition of clinical science.

In these lectures I shall describe some new methods of handling clinical evidence. These techniques have a statistical basis, and I have little doubt that my approach to clinical problems stems from my training and experience as a pharmacologist. Some are modifications of the techniques for the clinical trials of drugs which Professor Bradford Hill has pioneered in this country with such striking success.

In my first lecture I shall describe certain aspects of thyrotoxicosis. A few of the ideas are an extension of those put forward in the Bradshaw Lecture on "The Diagnosis of Thyrotoxicosis" (Wayne, 1954). I shall take the opportunity of indicating where further experience has reinforced or modified my views and shall also describe one or two new diagnostic techniques which have only recently become available. This lecture will also deal with the treatment of thyrotoxicosis, and especially with observations which were designed to make it possible to obtain statistically valid observations from a comparatively small number of cases. In this way we have been able to evaluate in a more precise way than has hitherto been possible the therapeutic effectiveness of various antithyroid drugs in man.

My second lecture deals mainly with the aetiology, diagnosis, and treatment of hypothyroidism and in particular with the relative incidence of the clinical features of the condition, but I shall also discuss the special problem of the diagnosis of Hashimoto's disease or auto-immunizing thyroiditis.

Profound alterations in body metabolism occur in both thyrotoxicosis and hypothyroidism. We have studied the effects of both conditions on total body water, total red-cell mass, total exchangeable electrolytes, and calcium metabolism, and I shall report our conclusions in brief and summary form.

In the five years since I went to Glasgow, where much of my time is occupied in teaching and administrative duties, it would not have been possible for me, without assistance, to carry out this work, and I am much indebted to all those who have collaborated with me, and especially to Dr. J. Crooks and Dr. I. P. C. Murray, who have taken a large and active share in these studies, and to Dr. R. A. Robb for his advice on the statistical aspects. I would also like to mention others who have contributed to the work I shall describe: Dr. M. M. Bluhm, Dr. James Buchanan, Dr. Watson Buchanan, Dr. F. P. Muldowney, and Dr. B. E. C. Nordin.

A Statistical Method Applied to the Clinical Diagnosis of Thyrotoxicosis

Though the diagnosis of thyrotoxicosis is often easy, there are many cases which give rise to uncertainty. This is especially so when the clinical picture is incomplete, or when atypical features are present, and in these circumstances even experienced clinicians may differ in their conclusions. Sometimes the same observer may alter his opinion on the same case on consecutive days. This state of affairs has always puzzled me, and the reason is not immediately obvious. It seems to depend on the nature of the mental processes involved in arriving at a diagnosis. In making his clinical

*The first of two Lumleian Lectures delivered before the Royal College of Physicians of London on April 14 and 16, 1959.

assessment a physician must first obtain a reliable history and elicit accurately the appropriate physical signs. At this stage we encounter "observer variation," since there is rarely complete agreement even among a group of experienced clinicians. Next, the physician must decide upon the relative importance he should attach to the diagnostically significant clinical features of the case. In so doing he falls back on his own experience or on that of his teachers. At this point further differences of opinion arise, due partly to the different degree of significance attached to certain features by different clinicians, and partly to the influence of a fortuitous run of positive or negative findings occurring towards the end of the clinical examination. It is because of these difficulties in making a diagnosis on clinical grounds alone that so many tests of thyroid function have been devised and are so widely used.

By using some of the principles of the statistical method known as discriminant analysis we have found it possible to increase the accuracy of the clinical diagnosis and also to study the effects of "observer error." The method consists in allocating to each clinical feature a positive or negative score, the value of which is based on analysis of the relative frequency of symptoms and signs in the disease. In this way a total score, or clinical diagnostic index, can be obtained in each case. There is a wide difference between these scores in frankly thyrotoxic patients and in normal persons, and in practice the index has proved helpful in distinguishing between toxic and non-toxic patients in cases presenting diagnostic difficulty. It also provides a numerical estimate of the degree of severity of the disease, which can be correlated with other indices of thyroid function.

We first studied 83 unquestionably thyrotoxic patients and 99 unquestionably non-toxic subjects, including in this group not only healthy persons but also patients with simple goitres, anxiety states, and post-menopausal symptoms. This group is termed "definite" in the tables and discussion. In each subject the presence or absence of the clinical features shown in Table I was recorded. These signs and symptoms were chosen because they had previously been shown by a clinical survey to differ in their incidence in thyrotoxic and in normal subjects (Wayne, 1954). In order to reduce the effects of "observer variation" the method of history-taking and the procedure for the physical examination were rigid. We have described our criteria elsewhere (Crooks *et al.*, 1959).

The Clinical Index

The clinical features recorded in the cases which had given rise to no clinical diagnostic difficulty were weighted by allocating a score to each (Table I). The positive or negative values of these scores were initially allocated on the basis of the relative diagnostic significance of each symptom and sign, as found by Wayne (1954) or, in a few instances, by Lerman (1948). These scores were then modified so as to diminish the effects of "observer variation." The total scores, which we call clinical diagnostic indices, were then calculated. These indices produced a good separation between non-toxic and toxic subjects; but the weighting factors for the individual clinical features were further modified to produce the widest possible separation between the two groups without reintroducing excessive "observer variation" effects. The indices were then recalculated. Fig. 1 shows the range of values obtained and the sharp separation between the toxic and non-toxic groups, so

TABLE I.—*Thyrotoxicosis—Clinical Diagnostic Index. Weighting Factors Allocated to the Symptoms and Signs of Thyrotoxicosis*

Symptoms of Recent Onset and or Increased Severity	Present Score	Score	Signs	Present Score	Absent Score
Dyspnoea on effort	+1		Palpable thyroid ..	+3	−3
Palpitations ..	+2		Bruit over thyroid ..	+2	−2
Tiredness ..	+2		Exophthalmos ..	+2	
Preference for heat (irrespective of duration) ..		−5	Lid retraction ..	+2	
Preference for cold	+5		Lid lag	+1	
Indifferent to temperature ..	0		Hyperkinetic movements	+4	−2
Excessive sweating	+3		Fine finger tremor ..	+1	
Nervousness ..	+2		Hands:		
Appetite increased	+3		Hot	+2	−2
,, decreased		−3	Moist	+1	−1
Weight increased		−3	Casual pulse rate:		
,, decreased	+3		Auricular fibrillation	+4	
			Regular rates:		
			<80 per minute		−3
			80 to 90 per minute ..	0	
			>90 per minute	+3	

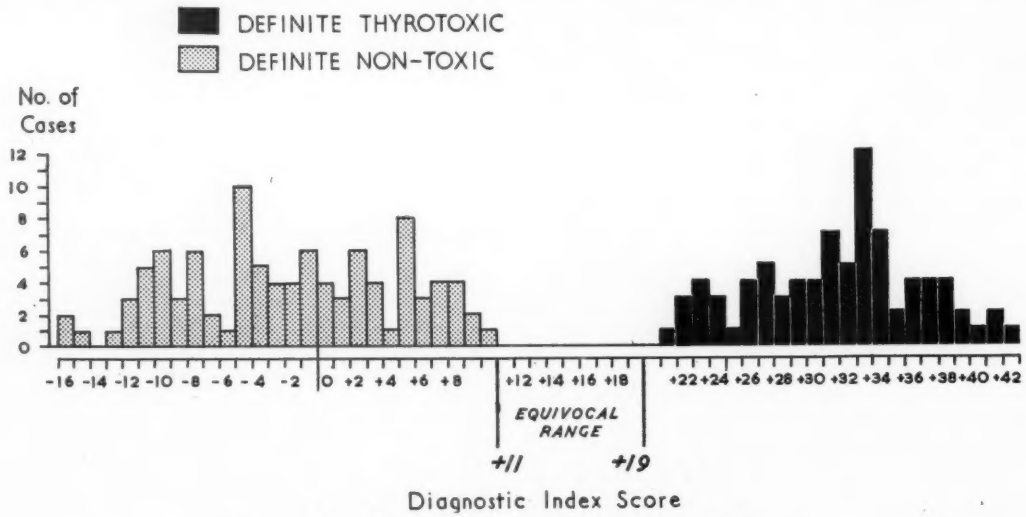

FIG. 1.—Clinical diagnostic index applied to cases in the definite group.

that an index of +20 or over indicated toxicity and one of +10 or lower that the patient was non-toxic.

We next studied a group of cases which were not obviously toxic or non-toxic. This group, which is subsequently called "doubtful," consisted of 118 cases, each of which had presented some diagnostic difficulty to one or more hospital physicians. All had been referred for radioactive iodine studies, and the final diagnosis was made only after prolonged observation, including the response to treatment. We were, therefore, confident of our final conclusions. At the patient's first visit the presence or absence of the symptoms and signs listed in Table I was recorded. Clinical diagnostic indices were calculated only when the final diagnosis was agreed after full investigation and the results of therapy were known. The distribution of the indices of the 118 patients in this group is shown in Fig. 2. A good division was still found between cases finally shown to be non-toxic and those shown to be toxic, 88% of their indices lying within the non-toxic and toxic ranges respectively. Thirteen subjects had indices lying between +11 and +19. We have called this the equivocal range. I shall mention these cases again later.

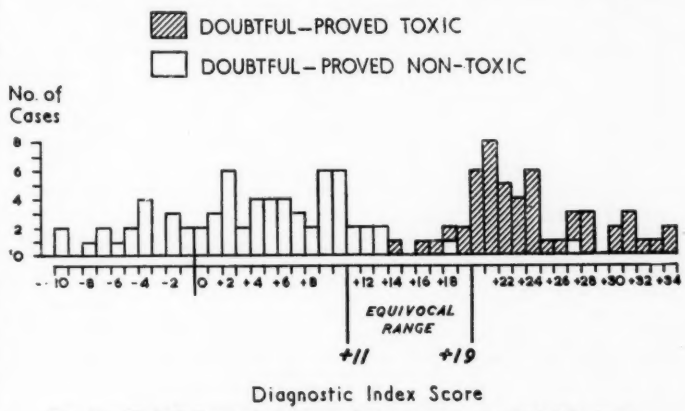

FIG. 2.—Clinical diagnostic index applied to cases in the doubtful group.

It thus seemed that in our hands the index was a reliable guide to the clinical diagnosis, but we could not be sure that it would be so when it was used by others. Fletcher (1952) has shown that competent physicians, investigating cases of emphysema, report widely different physical signs, and has emphasized the existence of "observer variation." We tried to limit the influence of this factor by formulating rigid definitions for the clinical features of thyrotoxicosis included in our index. But if it was to be generally applicable we knew we should have to investigate the results obtained by other clinicians. For this purpose we chose nine patients whose thyroid function had been difficult to assess clinically and nine observers co-operated with us. Analysis of variance of the results showed no significant difference in the score of seven of the nine observers. A medical student who had seen several cases of thyroid disease and who had received special instruction in the use of the scoring system was among the seven. The remaining two, who were both newcomers to the unit and had had no special experience of thyroid disease, recorded systematically lower scores. Nine further cases were used to make a comparison between the indices obtained by the physician who designed the score sheet and those allotted by a newcomer to the unit who had a wide experience of thyroid disease. There was no significant difference in their scores. These results suggest that no statistically significant difference will be obtained by observers using the diagnostic index provided they have some experience of thyroid disorders. Inexperienced observers tend to score low.

We have compared the relative diagnostic accuracy of the index with laboratory tests of thyroid function. Radioactive iodine studies were made on 202, and basal metabolic rate estimations were carried out on 188 of the 300 cases represented in Figs. 1 and 2. There was no statistically significant difference between the accuracy of the index and either radioactive iodine tests or basal metabolic rate estimations. In making this comparison, all the indices in the equivocal range between +11 and +19 were regarded as incorrect. We next applied the index to a further 50 patients, referred to us because they had given rise to diagnostic difficulty. We also asked three colleagues at three other hospitals in Scotland to use the index at their routine clinics and to compare the results with their final diagnosis. The total number of correct diagnoses made in this way was 149 out of 171 cases investigated—that is, 85%. Of the remaining 22 cases which were not correctly classified as toxic or non-toxic it is important to note that the diagnoses were completely misleading in only five subjects, or 3%. The remaining 17 all gave indices lying in the equivocal range, thus indicating the need for further investigation.

The cases which fall in the equivocal range are of special interest. In this group, when the final diagnosis is known, an examination of the individual features making up the index usually shows why difficulty has arisen and throws some light on the general problem of making a clinical diagnosis in thyrotoxicosis. Thus the non-toxic subjects in this group usually have severe anxiety states and have a high symptom score. In itself this is not usually sufficient to place them in the equivocal range unless they have in addition one or two heavily weighted signs such as goitre or tachycardia; several patients have had a previous thyroidectomy and the eye signs have persisted. The toxic subjects with scores falling in the equivocal range usually lack some diagnostic features which score highly; for example, a male patient who has neither goitre, bruit, nor hyperkinetic movements.

The clinical index can be used as a measure of the degree of severity of thyrotoxicosis, since it indicates the number of target-tissue effects, and, as might be expected, it correlates fairly well ($r=0.33$) with the basal metabolic rate (Fig. 3); it also correlates equally well ($r=0.36$) with both the four-hour uptake of radioactive iodine and the 48-hour protein-bound plasma radioactive iodine.

We believe that the clinical diagnostic index is a reliable and simple aid to diagnosis and is of value in day-to-day practice. It should be pointed out that our final decision on whether a patient was thyrotoxic or not was based on the response to therapy, and it follows that we define thyrotoxicosis as a condition in which antithyroid therapy produces a remission in the clinical features of the disease.

Lastly, I would emphasize that all clinical diagnosis involves the subconscious application of the principles underlying the method I have described. The clinician sifts and evaluates multiple symptoms and signs, and tries to select the clinical syndrome which best accounts for his findings. He attaches greater or less significance to the clinical features in the light of his past experience, and applies the technique of multiple correlation subconsciously in a non-quantitative manner. The clinical index applies this principle at the conscious level and makes a diagnosis less individual and more objective.

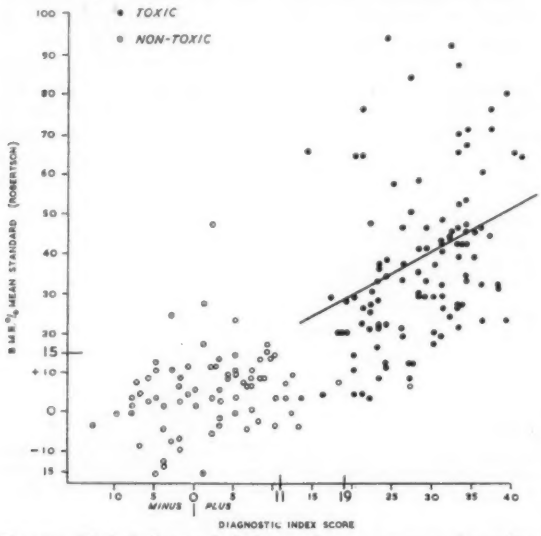

FIG. 3.—Clinical diagnostic index used as a measure of severity and correlated with the basal metabolic rate. The regression line of the index on the B.M.R. in toxic cases is shown.

Special Tests for Thyrotoxicosis

In my Bradshaw Lecture I reviewed the laboratory methods which have been used as diagnostic aids in thyrotoxicosis. Further experience has made me revise some of my views on their relative value and accuracy, and I shall give the reasons for this change of opinion and describe some new techniques which have been introduced.

Basal Metabolic Rate

This is the standard laboratory investigation used by most clinicians when they wish to confirm or refute a diagnosis of thyrotoxicosis. The basal metabolic rate (B.M.R.) is raised in a variety of other conditions—for example, in leukaemia, heart failure, and phaeochromocytoma. A complete list of diseases which may produce hypermetabolism and therefore misleading results is formidable (Bauer, 1956). In practice, however, the presence of these conditions is usually obvious and the estimation is not carried out. A thyrotoxic patient, however, may have a B.M.R. lying within the normal range, and Skanse (1949) refers to numerous studies which report the occurrence of normal rates in 10 to 20% of cases of thyrotoxicosis. At Sheffield we (Goodwin *et al.*, 1951) found that 35% of our cases had rates lying below +20% using the standards of Aub and Du Bois (1917). Further experience has modified my views on the degree of diagnostic inaccuracy in B.M.R. estimations. If the technique and standards advocated by Robertson and Reid (1952) are adopted, much more consistent and reliable readings are obtained. We have modified their techniques and we now carry out duplicate readings on at least two consecutive days. The patient stays in hospital overnight and is given full doses of butobarbitone. The lowest of the four values is adopted. With this method we have compared the diagnostic accuracy of the Robertson and Reid and the Aub and Du Bois standards in 209 subjects (Crooks *et al.*, 1958).

There is no difference in clinically obvious cases, but in doubtful cases which were subsequently proved to be thyrotoxic three-quarters were correctly placed by the former standards, compared with only half (taking the upper limit as +10%) or a quarter (taking the upper limit as +20%) on the Aub and Du Bois scale. Ten definitely thyrotoxic patients who had "normal" B.M.R.s by both standards were reinvestigated after treatment. In all of them the rate fell. In some this was probably due to the occurrence of the disease in patients whose B.M.R.s in health were much lower than the established mean value (Robertson, 1934). In at least half of the cases it was more probably due to obesity. Depot fat has a very low rate of oxygen utilization (Krebs and Johnson, 1948), so that obesity produces an increase in surface area without a proportional change in oxygen consumption. The incorporation of lean body mass in the reference standard has been shown by Bernstein *et al.* (1956) to eliminate this fallacy. In practice this finding suggests that a normal B.M.R. in a patient in whom there are grounds for suspecting thyrotoxicosis should not preclude the diagnosis if the weight approximates to height and age and there is a history of loss of weight.

Sleeping Pulse Rate

Though this is not strictly a laboratory test, I should like to discuss it here, since we always record the pulse rate while the patient is asleep under the influence of the hypnotic given before a B.M.R. estimation. In addition we have examined a larger number of readings taken by night nurses who had been carefully instructed on the technique they were to use. Details are given elsewhere (Crooks and Murray, 1958). The important findings are that sleeping pulse rates of more than 80 per minute make the diagnosis of thyrotoxicosis highly probable. There is, however, no significant correlation between the rate and the degree of clinical severity of the disease. Unfortunately, about a half of all the thyrotoxic patients studied had sleeping pulse rates of 80 per minute or lower, and this figure rises to two-thirds if diagnostically difficult cases only are considered. In 4 out of 138 cases of thyrotoxicosis sleeping pulse rates lower than 65 were recorded.

Chemical Estimation of Serum Protein-bound Iodine

The estimation of the amount of ^{127}I bound to protein is generally regarded as an accurate index of the amount of circulating thyroid hormone. Several workers in the United States of America have produced evidence that levels outside the normal range are the most reliable laboratory evidence of abnormal thyroid function. The subject is well reviewed by Rapport and Curtis (1950). We experienced serious technical difficulties with the method of Barker *et al.* (1951), but Macgregor and Farrell (1958) have introduced us to a modification of the method of Zak *et al.* (1952) which gives consistent and reliable results. It is, however, difficult to avoid

occasional contamination of glassware or chemicals by amounts of iodine greater than the extremely small quantities one is attempting to estimate. A room must be set aside for this determination, and all experiments must be performed in duplicate. The normal range is usually taken as 3.5 to 7 μg./100 ml. The level is raised in thyrotoxicosis, but mild cases usually show a lesser degree of abnormality than would be expected from the radioactive iodine criteria. The administration of either inorganic or organic iodine compounds affects the accuracy of the method. We have personally found it of value in assessing thyroid function in cases after thyroidectomy and when ^{131}I studies have given inconclusive results. This estimation, moreover, gives a more complete picture of iodine and thyroxine metabolism when the results of simultaneous studies with radioactive iodine are available (Riggs, 1952).

Radioactive Iodine

In my Bradshaw Lecture I described the use of ^{131}I as a diagnostic aid in thyrotoxicosis. It is now generally agreed that if the necessary equipment is available, tests using radioactive iodine cause the patient little inconvenience and give quick and relatively reliable answers. Macgregor and I (1958) have summarized our present views of the relative value of the different techniques using ^{131}I. It is clear that several techniques give results which correlate well with the final clinical diagnosis. The main recent advance in this field has been the introduction of the short-lived isotope ^{132}I, which delivers a much smaller amount of radiation to the gland. In addition, tests have been devised which distinguish between the high radioactive iodine uptake of thyrotoxicosis and of iodine-deficient glands.

At Glasgow we have used the same methods as at Sheffield and have studied two parameters of thyroid function. It is of some interest that the application of these techniques in a different department using different apparatus and controlled by different personnel and applied to a different population in a different country has given essentially the same results. We give 30 μc of the isotope by mouth and measure the four-hour uptake of ^{131}I by the gland and the 48-hour protein-bound plasma activity (P.B.^{131}I). The measurement of plasma activity has been rendered technically much easier by using an ion-exchange resin (Zieve *et al.*, 1956). Gland uptakes of greater than 45% and plasma P.B.^{131}I levels of more than 0.4% indicate thyrotoxicosis. When the results agree, and both indicate normality or abnormality, the correlation with the final diagnosis is of the order of 98%. About 10% of results are, however, discordant. When the gland uptake is raised and the P.B.^{131}I is within normal limits the patient usually has a non-toxic goitre.

When the gland uptake is within normal limits and the P.B.^{131} is raised it is wise to make sure that the patient is not suffering from Hashimoto's disease or has not been treated either by ^{131}I or by partial thyroidectomy. In such cases the functioning part of the gland may be working to the maximum of a diminished capacity to synthesize the thyroid hormones. There is a diminished thyroid pool, and a relatively large proportion of the circulating hormone is labelled with the isotope, giving a high P.B.^{131}I. In general, however, the 48-hour P.B.^{131}I correlates a little better than the gland uptake with the final diagnosis and it can be used as the sole diagnostic criterion. This test has the advantage that the isotope can be given to patients at hospitals far removed from the centre at which the estimations are carried out. By carrying out the thymol turbidity tests or colloidal gold reaction on blood showing significant plasma radioactivity it is sometimes possible to distinguish between samples from thyrotoxic patients and those from cases of Hashimoto's disease.

Our experience of the tests which use renal excretion of the isotope as an indirect measure of gland uptake suggest that the best is that of Fraser *et al.* (1953). Its only defect is the potential inaccuracy of urine collection. It has the merit that the patient need not come into contact with counting apparatus or technical personnel and that the dose of ^{131}I is relatively small. Two types of clearance test are used in this country. Pochin (1950) prefers the neck–thigh ratio at two hours and Coenegracht and Fraser (1955) have reported favourably on a method described by Berson *et al.* (1952). It gives an answer quickly, since it measures the ^{131}I clearance during the 35 minutes following the administration of the isotope, which must, however, be given intravenously. It is said to be the most reliable test in the assessment of cases which have been treated by thyroidectomy or ^{131}I (Goolden, 1958). We tend, however, to rely on the chemical estimation of P.B.^{127}I in such cases. The general problem of the relative reliability of methods of assessing thyroid function after ^{131}I therapy is discussed by Schultz and Zieve (1956).

Tests using radioactive iodine yield fallacious results if the patient is receiving iodine in the form of a cough mixture or Lugol's solution, and it is wise to perform a qualitative test for urinary iodide such as that described by Fraser *et al.* (1953) if unexpectedly low uptakes are recorded. Radiological contrast media which contain iodine may affect the uptake for many months. In practice, the most important fallacy in uptake tests comes from relative iodine deficiency. This may be associated with goitre or it may have been induced by the previous administration of an antithyroid drug. Thyrotoxic patients often have high uptakes for many months after treatment by thyroidectomy or by radioactive iodine. Fraser (1956) has described modified uptake techniques which in most of the above circumstances enable satisfactory results to be obtained using ^{131}I. We use these special tests comparatively seldom, since we find that, provided it is known whether the patient is receiving or has received treatment for suspected thyrotoxicosis, the two tests we use in combination almost always guide us to a correct result. When they are in agreement they are very reliable, and when they are discordant they give a warning that some other approach to the problem must be made. For example, in these circumstances we usually determine the B.M.R. or the P.B.^{127}I, or both. If there is still a doubt a therapeutic trial with an antithyroid drug should be carried out.

Use of ^{132}I

This isotope with a short half-life of 2.26 hours has recently become available. Its rapid decay enables studies to be carried out at frequent intervals, and its radiation effects are of such short duration that it can be used in children and during pregnancy. Compared with ^{131}I it gives only about one-fortieth of the radiation dose to the thyroid for an equivalent number of microcuries. At first, like Hanbury *et al.* (1954) we found it difficult to obtain consistent readings, but these

difficulties have now been overcome, and a new method of preparing the isotope from ^{132}Te, using an alumina column, obviates some of the hazards arising from the original technique, which involved distillation (Stang *et al.*, 1957).

^{132}I can be used in routine thyroid-function tests. Halnan and Pochin (1958) studied the neck–thigh ratio two hours after an oral dose taken fasting. They found a good separation between thyrotoxic and euthyroid subjects, and if there was doubt they repeated the test after the administration of thyroxine or triiodothyronine. Farran (1958) has shown that the rate of uptake of ^{132}I by the thyroid during the first 30 minutes after the intravenous injection of 3–5 μc. of the isotope is also a useful diagnostic test which gives a 90% separation between thyrotoxic and euthyroid cases. For detailed studies of thyroid function the short-lived isotope possesses great advantages over ^{131}I (Goolden and Mallard, 1958). It is, for example, specially suitable for use in investigations that require the repetition of tests, and can be used to study day-to-day variations in thyroid activity (Francois *et al.*, 1958; Halnan and Pochin, 1958) or to investigate the effect of antithyroid drugs on thyroid activity. This advantage over ^{131}I is well shown in Fig. 4, where the short-lived isotope

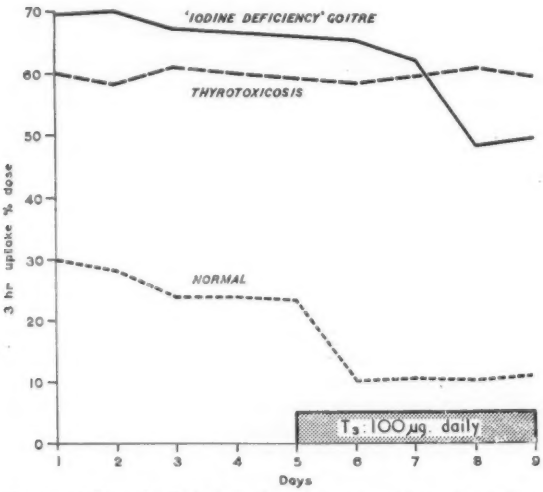

FIG. 4.—Effect of triiodothyronine on the thyroid uptake of ^{132}I in a normal subject, a thyrotoxic patient, and a patient with an "iodine deficiency" goitre.

has enabled daily estimations of the gland uptake to be made.

The suppression of the gland uptake of ^{132}I by triiodothyronine in the normal individual and in a case of non-toxic goitre is contrasted with the absence of effect in a thyrotoxic patient. The short-lived isotope is more difficult than ^{131}I to prepare and handle. Its chief defect from our point of view is that it cannot be used to estimate the plasma activity at 48 hours, which is the test of which we have most experience and on which we put most reliance. We agree with Goolden and Mallard (1958) that it is unlikely to replace ^{131}I completely in standard diagnostic work. We use it as they do in special investigations in which we wish to repeat our observations at frequent intervals. A more complete picture of iodine metabolism is obtained if estimations of P.B.^{127}I are carried out at the same time.

Treatment of Thyrotoxicosis

Three rival and satisfactory forms of treatment are available for treating thyrotoxicosis, and in a given case it is not always easy to decide which is the most appropriate. Surgical treatment is probably the most widely used. It has been made extremely safe by modern anaesthesia and by the pre-operative use of antithyroid drugs. Operation may, however, occasionally give rise to unfortunate sequelae. Thus, though rare, tetany from parathyroid damage, damage to the recurrent laryngeal nerve, wound sepsis, secondary haemorrhage, and adherent scars, as well as the pulmonary complications secondary to any surgical procedure, are still seen. The main criticism of surgery is the relative frequency with which patients relapse—a specially unfortunate occurrence if radioactive iodine treatment is not available, since a second operation is technically difficult and is especially liable to lead to hypothyroidism (Bartels, 1953). It is of interest that 10% of our series of 150 thyrotoxic cases treated by ^{131}I, and 12% of the 500 cases reported from Sheffield by Blomfield *et al.* (1959), were examples of recurrence of the disease after operation. The incidence of post-operative hypothyroidism is also high, ranging in different series from 2.9% to 21%, with a mean rate of 5.4% (Bartels, 1953).

It seems clear, therefore, that partial thyroidectomy is by no means the ideal form of treatment. The alternative methods involve the use of antithyroid drugs or of radioactive iodine. Much controversy surrounds the comparative effectiveness of different antithyroid drugs, and we have devised a method of comparison based on the history and physical examination which can be used to investigate this problem.

The Therapy Index

The clinician concludes that a patient is showing improvement when he observes the gradual disappearance of a number of abnormal symptoms and signs. This he can do fairly satisfactorily, but he finds that the degree of improvement is much more difficult to assess. For example, different clinicians may attribute different significance to any given change, and even the same observer may find it difficult to decide on the relative importance to be attached to conflicting features—for example, to a persistence of tachycardia in a patient who has gained weight. The alternative method of assessing improvement by repeated estimations of the B.M.R. is time-consuming and inconvenient to the patient. The normal range of B.M.R.s is so wide that it is difficult to know when a given patient has reached the level which is normal for her, and a comparison between various forms of treatment must be based on statistical differences between groups of patients.

We have approached the problem of assessing the response to treatment in a new way. We have modified the clinical diagnostic index, which I have already discussed, so that it can be used as a therapy index. To do this we have removed from the list of the diagnostic features of thyrotoxicosis those which are unaffected by treatment. The scores used for this purpose are given in Table II. It will be seen that the figures differ in some respects from those given in Table I for the diagnostic index. For example, the combination of loss of weight with increased appetite is highly significant diagnostically, but in the assessment of therapeutic response an increase in weight is more

TABLE II.—*Thyrotoxicosis—Therapy Index. Weighting Factors Allocated to the Symptoms and Signs of Thyrotoxicosis*

Symptoms	Score	Signs	Score
Dyspnoea on effort ..	+1	Hyperkinetic movements	+4
Palpitation	+2	Fine finger tremor ..	+1
Tiredness	+2	Hands:	
Preference for cold ..	+5	Hot	+2
Excessive sweating ..	+3	Moist	+1
Nervousness	+2		
Appetite increased ..	+1	Resting pulse rate:	
Weight decreased*	+4	>85/minute	+3

* For each 4 lbs. weight gain deduct 1 point.

important than a diminution in appetite. Hence the rating for loss of weight was increased to +4 and that for increased appetite reduced to +1. Patients were examined weekly in the out-patient department by the same clinician, and a standard routine was used. The resting pulse rate was recorded after the patient had been lying undisturbed on a couch for 10 minutes. The total score or therapy index was derived at the first visit and was determined at each subsequent weekly visit. A symptom or sign had to disappear completely before its value was deducted from the index.

Application of the Therapy Index

We first studied 40 patients who were definitely but not severely thyrotoxic and who had diffuse goitres and exophthalmos; that is to say, they were examples of classical Graves's disease. They were allocated alternately to two groups. Those in the first group were given methylthiouracil in a dose of 600 mg. a day for two weeks, followed by 300 mg. a day; those in the second group had 600 mg. of potassium perchlorate a day.

Typical examples of the changes in the index during treatment are shown in Fig. 5 (A and B) along with the changes in the B.M.R. A response of this type with a linear regression on time was shown by 33 out of the 40 patients. The other patients were slower to respond

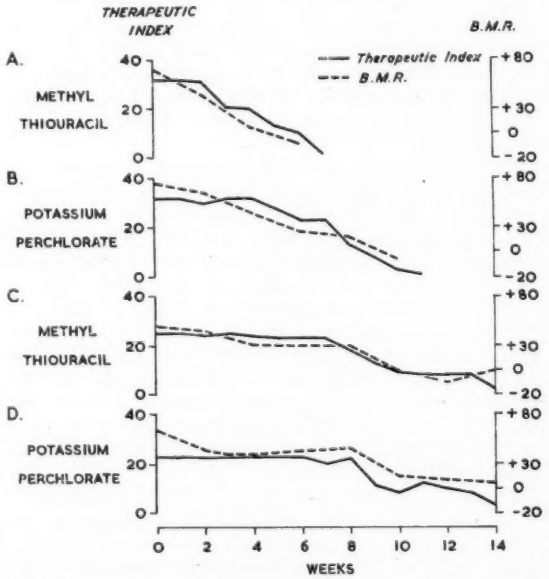

FIG. 5.—Changes in therapeutic indices and B.M.R.s during treatment with methylthiouracil and potassium perchlorate (600 mg. daily). A and B show linear changes of the therapeutic indices with time. C and D show the delayed type of therapeutic response.

to the drugs as judged by the changes both in the index and in the B.M.R. Typical examples are shown in Fig. 5 (C and D). This also shows that a failure to respond immediately to an antithyroid drug does not preclude ultimate control.

Average rates of change were not used to compare the drugs, since they do not represent accurately the influence of the cases showing the slow type of response. An alternative method of comparison was therefore devised, and we determined the time taken for all the patients in each group to reach a level which we decided would indicate complete remission or "cure." This was taken to have occurred when the therapy index reached and remained within the range zero to 5 for three consecutive weeks. The actual week of "cure" was chosen as the week with the lowest of the three values. The range of indices from zero to 5 was chosen because it allows only one feature of high diagnostic significance to be present. We found, moreover, that, in patients satisfactorily controlled the indices fluctuated for long periods between zero and 5. Further

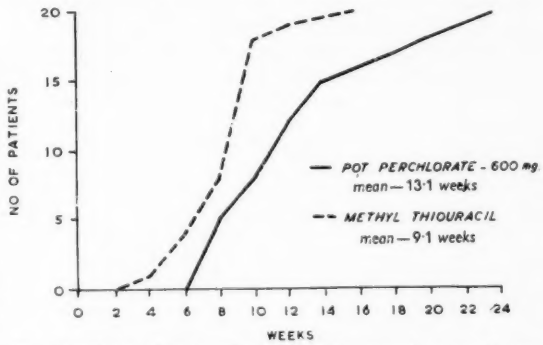

FIG. 6.—Times taken to effect "cure" by potassium perchlorate (600 mg. daily) and methylthiouracil.

confirmation that this range indicated full control of the disease was afforded by estimations of the B.M.R. in the two groups. When examined statistically the mean rates at the time of "cure" did not differ significantly from zero.

Fig. 6 shows the number of patients reaching the level we have defined as "cure" at any given time. From it can be calculated that the mean time to "cure" for the group receiving methylthiouracil was 9.1 weeks, and for that receiving potassium perchlorate 13.1 weeks.

When these patients were euthyroid they were given maintenance therapy for three months, and then the administration of the drugs was stopped. Of the 40 cases, 14 relapsed and were regarded as a separate group. Eight subjects who had received methylthiouracil were now given potassium perchlorate and six subjects previously treated with perchlorate were re-treated with methylthiouracil. The design of this series of observations was similar to that of the "cross-over" method used by pharmacologists for the assay of substances such as insulin. In the group receiving potassium perchlorate the time taken to effect a "cure" was four weeks longer than when they had been given methylthiouracil. Similarly, the group receiving methylthiouracil reached the score indicating a "cure" four weeks earlier than when they had been given potassium perchlorate. In these observations each patient acted as her own control.

We also made a comparison between the initial values of the therapy index and the times taken to effect "cure." This showed no significant correlation between the two variables. In other words, there is no relationship between the initial severity of the disease and the rate of therapeutic response. This runs counter to the generally accepted but unproved view that severe cases of thyrotoxicosis take longer to become euthyroid than mild ones.

Comparison of Methylthiouracil, Carbimazole, and Potassium Perchlorate as Antithyroid Drugs

We were now satisfied that our clinical method of comparison gave valid results and that it was unnecessary to check the patient's progress by repeated estimations of the B.M.R. It was thought sufficient to carry out this test only at the start and at the end of the trial. Two further groups of patients with classical Graves's disease were treated, one with potassium perchlorate in a dose of 1,000 mg. a day and the other with carbimazole in a dose of 60 mg. a day for two weeks followed by 30 mg. a day—that is, in one-tenth of the dose received by the group which had received methylthiouracil. The cumulative distribution for both drugs is shown in Fig. 7. The mean time to

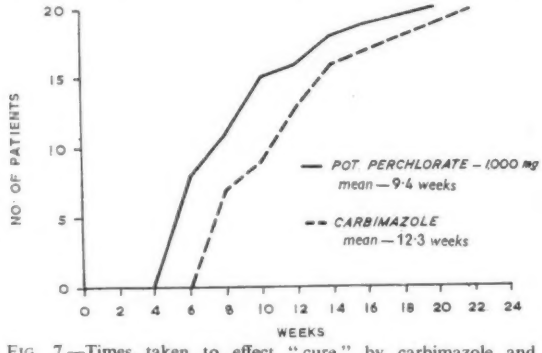

FIG. 7.—Times taken to effect "cure" by carbimazole and potassium perchlorate (1,000 mg. daily).

"cure" for the potassium perchlorate treated group was 9.4 weeks and for the carbimazole series 12.3 weeks. Variance analysis of the mean times to "cure" of the four series of 20 patients receiving different drugs or different doses of perchlorate showed that methylthiouracil (600 mg. daily for two weeks followed by 300 mg. daily) and potassium perchlorate (1,000 mg. daily) were equally effective; both were more effective than carbimazole in one-tenth of the dose of methylthiouracil and potassium perchlorate in a dose of 600 mg. a day.

When we first began to use potassium perchlorate we were impressed by its relative freedom from unwanted side-effects. It was first shown to be a useful antithyroid drug by Godley and Stanbury (1954). This was confirmed in a much larger series of cases by Morgans and Trotter (1954), who had the impression that the rate of response produced by 400 mg. daily was less than that produced by methylthiouracil in a dose of 200 mg. daily. Since potassium perchlorate is a simple inorganic compound it seemed to us *a priori* less likely to produce sensitization effects than the organic antithyroid substances and in particular to be less likely to damage the haemopoietic system. We decided, therefore, to try to assess the relative frequency of the side-effects of potassium perchlorate, methylthiouracil, and carbimazole. No statistically significant difference was found between the liability of the organic substances to produce sensitization reactions such as skin rashes or blood dyscrasias (Table III). On the other hand potassium perchlorate in doses of 1,000 mg. a day or under was less likely than the organic antithyroid compounds to produce adverse effects of this type. Higher doses of potassium perchlorate produced reactions as often as the organic compounds. Of the four patients who complained of nausea while taking perchlorate three were able to continue when an antacid was given, and the nausea disappeared within a week.

TABLE III.—*Toxic Effects in Cases Treated With Methylthiouracil, Carbimazole, and Potassium Perchlorate*

Toxic Effect	Methyl-thiouracil 600 mg. Daily 2 Wks. then 300 mg. Daily	Carbimazole 60 mg. Daily 2 Wks. then 30 mg. Daily	Potassium Perchlorate	
			600 mg.* or 1,000 mg.	1,500 mg.† or 2,000 mg.
No. of cases ..	151	85	200	50
Skin rashes ..	5	4	1	5
Nausea	—	1	3	2
Drug fever ..	2	—	—	—
Agranulocytosis ..	2	2	—	1
Thrombocytopenia	1	—	—	—

* 35 patients. † 10 patients.

We draw two generalizations from our observations. Both the rate of response to antithyroid drugs and their liability to produce sensitization reactions seem to vary with the dose. We have examined the extensive literature on the antithyroid drugs and have found it extremely difficult to assess the significance of the results reported. In comparing the relative activity of different compounds few observers seem to have been aware of the complexity of the problem. Not only must the clinician know about and allow for the phenomenon common to all biological material of individual variation in response, but he must also standardize, so far as he can, the type of patient he treats and the doses he uses. We have found no published observations which cannot be explained on the view that the response of a patient to an antithyroid drug is a function of the dose. At a certain critical blood level, which is different for each drug, the synthesis of the thyroid hormone is completely blocked and all drugs are equally effective when given in a dosage which will produce this or a greater level.

This immediately raises the question of the relative liability of the different drugs to produce toxic side-effects at different dosage levels. We have also examined the extensive literature on this subject. It is impossible to draw definite conclusions. Few clinicians have compared properly matched groups of patients under their own observation on standard doses of different drugs, and when they have done so, statistical tests of significance have rarely been applied to the figures. Most of the conflicting conclusions can be traced to one or other of these defects. We do not think it justifiable, as many have done, to draw deductions from groups of cases collected from the literature.

Our own tentative conclusions are these. There is no convincing evidence that any of the organic antithyroid drugs is significantly more toxic than any other when given in therapeutically equivalent dosage. Our experience suggests that potassium perchlorate is less likely to give rise to skin rashes or blood dyscrasias in doses which act as quickly as the conventional therapeutic doses of methylthiouracil and carbimazole.

Use of Potassium Perchlorate as an Antithyroid Drug

Since our investigations suggested that potassium perchlorate was the antithyroid drug of choice I should like to deal briefly with one or two practical aspects of its use. It affects the iodide-trapping mechanism of the thyroid, and there is evidence that the action of substances of this type can be overcome if sufficient iodide is given (Franklin *et al.*, 1944). We therefore made observations on groups of patients with relatively high and relatively low intakes of iodine in the diet. There was no statistical difference in the rate of response to perchlorate. There is thus no need to advise dietetic restriction of iodide intake, though we warn the patient against taking certain cough medicines which contain iodide in relatively large amounts.

We have used potassium perchlorate pre-operatively in 20 patients, of whom 18 had nodular goitres of moderate size, and our surgical colleague Mr. D. H. Clark did not encounter technical difficulties due to increased vascularity in this type of case. It may well be that the contradictory views which have been expressed on the effects of antithyroid drugs on the vascularity of the gland are due to the lack of an investigation designed to eliminate the effects of biological variation and of bias on the part of the surgeon.

Potassium perchlorate has been given to nine pregnant thyrotoxic patients and in each case satisfactory control of the disease was achieved. One of the infants had a very slight enlargement of the thyroid gland which disappeared within six weeks.

We now use potassium perchlorate in a dose of 250 mg. four times a day as our standard antithyroid drug, and so far we have had no reason to regret our choice.

Reserpine in Treatment of Thyrotoxicosis

Canary *et al.* (1957) have claimed striking improvement in thyrotoxic patients treated with reserpine. Ten patients who were given 0.25 to 1 mg. of the drug orally every six to eight hours improved considerably in three weeks. Palpitation, excessive sweating, heat intolerance, dyspnoea on exertion, the skin manifestations, and tremor were completely relieved in all the members of the group, and nervousness improved in all but one. Eye signs disappeared in three patients and improved in two. The gland's uptake of radioactive iodine, however, was not affected. Others (Moncke, 1955; Lövei and Bona, 1956; Chowdhury, 1958) have also claimed that reserpine is of value in the treatment of thyrotoxicosis, and Gordan (1958) states that since the publication of the paper by Canary *et al.* almost all the thyrotoxic patients he has seen have been treated with this drug.

Reserpine diminishes the results of sympathetic overactivity partly through central and partly through peripheral mechanisms. There are thus theoretical reasons why it might diminish the effects of an excess of thyroid hormone, since this may produce some of its peripheral actions by sensitizing the tissues to adrenaline and noradrenaline.

We did not feel justified in using this potentially toxic substance as an alternative to a standard antithyroid drug. We decided, however, that it might be given with advantage to patients immediately after the administration of radioactive iodine. It would then have its effect in the latent period before the isotope had begun to depress thyroid function. This is a period in which in our view the administration of drugs which affect thyroid function is undesirable.

A double-blind trial was used, but, since the side-effects of reserpine might have enabled the observers to differentiate between the groups receiving the reserpine and the inert tablets, a second observer was interposed. Part of the interest of this trial lies in the use of this method, which could be applied to the evaluation of any toxic drug. That this precaution was necessary is demonstrated by the high incidence of severe toxic effects which occurred in the group receiving reserpine.

Twenty patients who had received ^{131}I therapy took part in the trial. They were allocated by random selection to two groups, one of which received reserpine by mouth in a dose of 0.5 mg. four times a day and the other inert tablets of identical appearance. They were interviewed by a physician who recorded the blood-pressure and supplied the tablets, and who noted any symptoms or signs which either he or the patients attributed to the tablets. The patient was then told to withhold this information from the second physician, who assessed the degree of thyrotoxicosis.

Progress was judged by the weekly assessment of those symptoms and signs which improved in the cases treated by Canary *et al.* (1957). Neither at four weeks, the time at which Canary *et al.* made their observations, nor at six weeks was there any difference between the two groups in the number of clinical features recorded except in the case of the pulse rate and weight. There was a significant fall in the pulse rate ($P<0.01$) and a significant gain in weight ($P<0.05$) in the reserpine-treated series. Full details of this work have been published elsewhere (Buchanan *et al.*, 1959).

It is a remarkable and rather disturbing fact that so toxic a substance can have been widely used in the treatment of a disease for which much safer and more specific remedies are available. It is all the more remarkable when a controlled trial shows that reserpine administered orally in doses apt to give severe side-effects produces no obvious benefit in a group of thyrotoxic patients. Indeed, the only alterations in our series which could be attributed to reserpine were due to a non-specific action of the drug. Clinicians have no doubt been unduly impressed by the increase in weight and the slowing of the pulse rate which reserpine produces in thyrotoxic patients. When these are secondary to a diminished amount of circulating thyroid hormone they undoubtedly indicate improvement in the disease. But reserpine can produce these effects in euthyroid individuals, and in themselves they confer no special benefit on the patient. The thyrotoxic patient given deoxycortone and salt would put on weight, but this could hardly be regarded as evidence that it was a valuable form of treatment.

We conclude that reserpine has no place in the treatment of thyrotoxicosis except possibly in a thyrotoxic crisis, where different considerations apply.

Radioactive Iodine in Treatment of Thyrotoxicosis

It is universally agreed that ^{131}I is effective in the treatment of thyrotoxicosis, and there are some who believe that it is the best and safest form of treatment for every case of the disease. The majority of centres, however, use this form of therapy only in selected cases. There are several excellent recent reviews of this subject (Myant, 1956; Pochin, 1958; Blomfield *et al.*, 1959), and I do not propose to cover the same ground. I shall outline our own criteria for the selection of cases and

the simplified method we use for deciding on the dose of the isotope. We have compared the results of our technique with those of more complex methods, and in addition have made observations on the influence of pre-treatment with methylthiouracil on the radio-resistance of the thyroid gland.

Selection of Cases

The chief consideration which limits the use of ^{131}I in the treatment of thyrotoxicosis is fear of the late development of malignant changes in the thyroid gland. Many thousands of patients have been treated in the past 15 years and so far there are no reports of cases of carcinoma which could be attributed to this form of treatment. There is, however, evidence that ionizing radiations can lead to the development of malignant disease of the gland in children (Wilson *et al.*, 1958). It seems improbable that the incidence of post-radiation carcinoma in the adult, if it occurs at all, will be high. Most clinicians, however, prefer to treat patients with an expectation of life of 20 to 25 years. Younger patients may be treated if surgery is contraindicated. In women before the menopause and in comparatively young men the possibility of genetic effects arising from irradiation of the gonads should be taken into account (Blomfield *et al.*, 1959).

These general considerations lead us to select the following groups of patients as suitable for treatment with ^{131}I. (1) Patients over the age of 45 in whom it is the treatment of choice. (2) Any patient who, because of associated disease, has a life expectancy of less than 20 years. (3) All patients, irrespective of age, who have relapsed following thyroidectomy. A second operation is specially apt to produce myxoedema or damage structures adjacent to the gland. (4) Young patients who have relapsed following antithyroid drugs or who have shown sensitization reactions to them but only if they have refused operation.

The only absolute contraindication to ^{131}I is pregnancy. A few workers are unwilling to treat a case with a multinodular gland, especially if there is tracheal compression. As a rule, however, such cases fulfil our criteria of suitability, and in our experience ^{131}I therapy gives satisfactory results.

Methods of Deciding on Dosage of ^{131}I

The selection of the appropriate dose of ^{131}I is important. It is the aim of the physician to find a dose which will cure the patient without producing hypothyroidism. A few centres give small and repeated doses of the isotope, hoping thus to minimize the possibility of overtreating the case (Williams *et al.*, 1949). The majority, however, emulate the surgeon and try to give a single dose which will destroy the optimum amount of functioning tissue. In general they are no more and no less successful than the surgeon, and the overall incidence of myxoedema in 1,720 cases from different centres was 9% (Seed and Jaffé, 1953). In the investigation carried out in Sheffield we attempted to deliver to the thyroid gland a dose of between 6,000 and 8,000 rads (Blomfield *et al.*, 1955). We used a formula which involved a knowledge of the 48-hour uptake of a tracer dose of ^{131}I and of the weight of the gland. A review of 140 cases showed that 62% of patients were made euthyroid with one therapeutic drink and ultimately 84% were cured; 12% showed evidence of hypothyroidism. One member of this team went to Edinburgh and reported the results of treating 150 cases of thyrotoxicosis using a greatly simplified dosage scheme (Macgregor, 1957). The results did not differ significantly from those obtained by using the more elaborate and quantitative technique described above.

In Glasgow we have used a similar dosage scheme. To patients with glands which could not be palpated we have given 5 mc., to those with definite diffusely enlarged but small glands 6 to 7 mc., and to those with larger glands doses up to 25 mc. Factors other than gland size have influenced our decisions on dosage; for example, patients who had a previous thyroidectomy received relatively small doses, usually between 5 and 6 mc., while those with nodular glands and patients with cardiac failure received relatively large doses. All patients were seen at monthly intervals and were retreated three to four months after the initial dose if they were still thyrotoxic. After they had become euthyroid they were seen at intervals of from two to six months. Hypothyroidism was treated only after it had persisted for from three to four months.

The results of treating by this method a series of 100 cases followed for a minimum period of 12 months is shown in Table IV. For comparison we give the figures

TABLE IV.—*Clinical Results of Radioactive Iodine Therapy (Minimum Follow-up, One Year)*

	Present	Macgregor (1957)	Blomfield *et al.* (1959)
No. of cases	100	150	500
Euthyroid with one dose	67%	59%	59%
Myxoedema	6%	9%	12%

for a much larger series of 500 cases reported from Sheffield by a different group of workers (Blomfield *et al.*, 1959) and for the 150 cases to which we have already referred, treated at Edinburgh by Macgregor (1957). There is no significant difference in the figures for the one-dose cure-rate or for the incidence of hypothyroidism. It should, however, be remembered that our minimum follow-up period of one year underestimates the incidence of hypothyroidism which may develop several years after treatment.

We, however, had also determined the 48-hour uptake of ^{131}I and estimated the size of the gland in grammes, so that we were able to calculate the dose we would have given if we had been using the more precise Sheffield technique. This alternative dose was not calculated until after treatment so as to avoid any bias in the original dose prescription. We have plotted the doses we actually used against those which would have been given if we had used the Sheffield procedure. Fig. 8 shows that we have tended to give larger doses to those in the small-dose range and smaller doses to those in the large-dose range. This phenomenon is probably due to the reluctance of those using the clinical method of dose prescription to prescribe very large doses in the absence of the moral support of a formula. The difference is, however, not reflected in the one-dose cure-rate probably because of the relatively small numbers of patients who required large doses, and also because these patients tend to be under-treated even when the more precise method is used (Blomfield *et al.*, 1959).

We agree with Macgregor that the prescription of an entirely accurate radiation dose is not possible partly because of errors inherent in the technique for the estimation of the gland mass, partly because of differences in the behaviour of the tracer and therapeutic

doses, and partly because of the biological variability in the radiosensitivity of different glands. With his method thyrotoxic patients can be treated safely and effectively without elaborate techniques. Though we do not allow for the percentage uptake of ^{131}I by the gland in deciding on the dose to be given, we consider preliminary tracer investigations desirable to confirm the diagnosis.

Pre-treatment of thyrotoxic cases with methylthiouracil and thyroxine before giving ^{131}I has been used by Fraser *et al.* (1954) to produce a more uniform uptake of the isotope by the gland. We investigated the effects of pre-treatment with methylthiouracil on the results of ^{131}I therapy. A series of 28 cases treated with methylthiouracil until one week before the ^{131}I was administered provided a significantly smaller number of one-dose cures (28%) than a comparable series which received no premedication (75%). Further investigations have shown that this effect is probably due to an increased degree of resistance to radiation conferred on the gland by the pre-treatment. This factor must be taken into account whatever scheme of dosage is used, and further observations suggest that a dose at least 25% larger must be given to those who have recently received methylthiouracil.

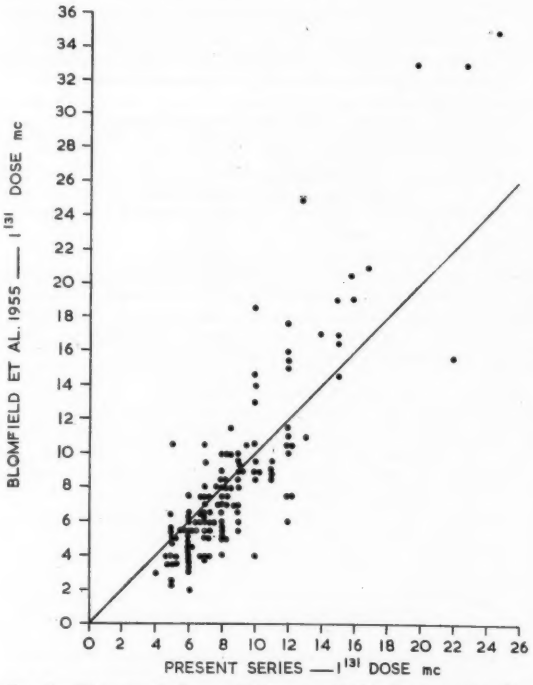

FIG. 8.—Therapeutic doses of ^{131}I, prescribed in the present series, plotted against doses calculated from the formula of Blomfield *et al.* (1955). The oblique line has been drawn at 45 degrees to the ordinates.

Choice of Treatment

No hard-and-fast rules can be laid down, but the clinician will show wisdom if he takes advantage of ^{131}I treatment when it is available and uses it to treat patients whose disease has recurred after operation and those with heart disease. It is of course much the most pleasant form of treatment, and if I were to become thyrotoxic it is the form I would choose. Younger patients are usually best treated in the first instance with a course of an antithyroid drug such as potassium perchlorate. Those who relapse should be advised to have a thyroidectomy after they have been rendered euthyroid by a further course of an antithyroid drug.

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[*The Second Lecture will be published next week, with the list of references.*]

REVERSAL OF ANTIBIOTIC RESISTANCE IN HOSPITAL STAPHYLOCOCCAL INFECTION

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There is much evidence to suggest that some at any rate of the multiple-resistant strains of *Staph. pyogenes* so prevalent in our hospitals to-day are of enhanced virulence, both in their capacity to initiate infection and in the severity of the infection produced. Thus, although such strains are relatively uncommon among staff carriers, they are responsible for the majority of cases of post-operative infection (Alder *et al.*, 1955; Barber and Burston, 1955; Shooter *et al.*, 1958), and some investigators have reported that infection with "hospital staphylococci" may be of unusual severity (Rountree and Freeman, 1955; Beaven and Burry, 1956; Ede *et al.*, 1959). While it cannot be assumed from this that multiple resistance and enhanced virulence are necessarily associated, the process of selection of drug-resistant staphylococci in hospitals may have tended to select strains of high virulence. In fact, nearly all the multiple resistant staphylococcal infections in hospitals to-day are due to a relatively few strains of *Staph. pyogenes* most of which belong to phage group III or type 80.

The principles for preventing hospital cross-infection enunciated long before the introduction of antibiotics remain the same to-day, but the ubiquity of the staphylococcus makes their strict application difficult in relation to this microbe. It is possible that pathogenic staphylococci could be kept at bay if we had sufficient isolation facilities, but at present this is not the case in most hospitals in Britain.

It seemed reasonable, therefore, to attempt to break the vicious circle by introducing a controlled antibiotic policy, designed to inhibit the emergence of drug-resistant staphylococci and to favour penicillin-sensitive strains. The present investigation was undertaken to

*Working with a grant from the Medical Research Council.

study the effect of such a policy, in association with the strict application of a number of anti-cross-infection measures introduced six months prior to the antibiotic policy.

Scope of Investigation

The incidence and drug-resistance of all staphylococcal infections in the surgical wards of a large general hospital have been studied over the period October 1, 1957, to June 30, 1959. Seven wards were involved in the study: two female and two male general surgical wards, one female and one male ward primarily devoted to orthopaedic patients, and one male urological ward. The ward units consist of open wards with 15 to 24 beds, plus one to three side-wards. During the course of the investigation a total of 5,239 patients were admitted.

Anti-Cross-Infection Measures

A cross-infection committee was set up in the hospital in April, 1957, and in the ensuing six months a number of measures were introduced to reduce hospital cross-infection. The most important of these were as follows:

1. *Isolation,* wherever possible, and barrier-nursing of patients with multiple-resistant staphylococcal infection. As a policy this was only partially effective for two reasons. Firstly, isolation was not instituted for at least 24–48 hours after the onset of infection, since the criterion depended on a bacteriological report. Secondly, since the number of side-wards was small one was not always available. For this reason isolation of all patients with infections, whatever the antibiotic sensitivity, was quite impracticable.

2. *Laundry Procedures.*—All sorting of dirty linen in wards was abandoned. The laundering of blankets between patients was instituted and all blankets were treated with a quaternary ammonium compound in the rinse. Frequent laundering of curtains, which surround most of the beds, was recommended, and these also were treated with a quaternary ammonium compound.

3. *Hospital Sterilization.*—All autoclaves and their use were thoroughly checked and where necessary improvements introduced.

4. *Ward and Theatre Hygiene.*—Attempts were made by means of discussions, lectures, and general propaganda to keep ward and theatre hygiene at a high level.

5. *Ward Closure.*—On two occasions during the investigation a ward was closed because of an outbreak of staphylococcal infection.

Antibiotic Policy

The essential features of the antibiotic policy were restriction in the use of all antibiotics for prophylactic purposes, strict limitation of the use of penicillin, and the general employment of double chemotherapy, each drug being given in full dosage. A total ban on penicillin was clearly impossible, since it is the antibiotic of choice for a number of infections. Its use was therefore confined to two medical and two surgical wards, and the nursing staff of these wards were supplied with cartridge syringes and taught to give injections of penicillin without spraying penicillin into the atmosphere (cf. Gould, 1958).

The policy was put into operation at the beginning of April, 1958, and all medical officers were individually circulated with the following instructions:

1. *General Restriction in Use of All Antibiotics.*—In particular the following only to be used where there is *definite* indication that they are likely to be of benefit to the patient: penicillin, streptomycin, tetracyclines (chlortetracycline, oxytetracycline, and tetracycline), chloramphenicol, erythromycin, and novobiocin.

2. *Abandonment of Penicillin,* except in the following wards: B5, B6, C3, C4. (Wards B5 and B6 are medical wards and are not referred to in this study. Wards C3 and C4 are the two wards devoted primarily to orthopaedic cases.) Where an exception to this rule is made, patient must be in a *side-ward.* All penicillin injections to be given with special precaution to prevent aerial contamination.

3. *Use of the Chemotherapeutic Agents in Combination,* wherever possible, and *always* when one of the antibiotics listed in paragraph 1 is being used.

4. Local application to be carried out only with preparations not suitable for systemic administration—for example, neomycin, bacitracin, polymyxin, chlorhexidine.

During the course of the investigation cross-resistance between chloramphenicol and erythromycin was noted (cf. Barber *et al.,* 1958), and in January, 1959, the following was added to item 3: *Combination of Chloramphenicol and Erythromycin should be avoided.*

A list of conditions for which penicillin was the drug of choice was appended, together with the following recommendations of suitable combinations for the types of infection most frequently encountered in the hospital:

I. MEDICAL WARDS

Respiratory Infections
- *Acute pneumonia:* Sulphonamides, if necessary with chloramphenicol, or tetracycline, subject to bacteriological findings.
- *Chronic bronchitis:* Combinations of tetracycline, sulphonamides, and chloramphenicol; *neomycin inhalation.*

Intestinal Infections:
- *Bacillary dysentery:* Sulphonamides, polymyxin.
- *Salmonella infections:* Chloramphenicol and sulphonamides.
- *Amoebiasis:* Oxytetracycline.
- *Diverticulitis:* Sulphonamides, when necessary.
- *Meningitis* { Meningococcal: Sulphonamides. / *H. influenzae:* Chloramphenicol and streptomycin.
- *Brucellosis:* Tetracycline and streptomycin.

Urinary Infections: Pyelitis, pyelonephritis, cystitis, etc., dependent on bacteriology, including sensitivity tests.

Skin Infections: Topical application of neomycin, bacitracin, polymyxin, chlorhexidine, in various combinations.

Lymphogranuloma: Sulphonamides and tetracycline.

II. SURGICAL WARDS

A. **Prophylaxis:** No antibiotics except for the following:
- *For Chest: None,* unless purulent bronchitis present at time of operation; if so, tetracycline and chloramphenicol.
- *Cardiac Surgery* (arterial grafts, etc.): Penicillin, streptomycin, and chloramphenicol for four days.
- *Insertion of Foreign Bodies* (e.g., bone grafts, etc., hernias): As for cardiac surgery.
- *Compound Fractures:* Chlortetracycline and chloramphenicol.
- *Craniotomy and Laminectomy:* Sulphonamides and chloramphenicol. Possibility of sprays in local application to be investigated.
- *Burns:* Local application of neomycin and polymyxin with bacitracin or chlorhexidine. Very extensive burns: systemic tetracycline and erythromycin.
- *Skin Grafts:* No antibiotic cover if clean.
- *Bowel Surgery:* Neomycin-bacitracin capsules or phthalylsulphathiazole and neomycin.

B. **Treatment.** *Peritonitis* (e.g., with burst appendix, infected gall-bladder, pancreatitis, etc.): Tetracycline and either erythromycin or novobiocin, pending bacteriological investigation.

Paediatrics

Neonatal: Staphylococcal infection, erythromycin and novobiocin, subject to bacteriological reports. Local treatment with neomycin and bacitracin, or sulphacetamide in eye infections with staphylococci.

Older Children: Acute respiratory infections: Tetracycline and sulphonamides.

Changes in Antibiotic Consumption Following the Antibiotic Policy

Comparison of the figures for consumption of antibiotics in the hospital in the year April, 1957, to March, 1958, and those in the year April, 1958, to March, 1959, has shown that after the introduction of the antibiotic policy the following changes in consumption occurred: penicillin, ÷2.6; tetracycline, ×1.8; chloramphenicol, ×2.0; erythromycin, ×2.5; novobiocin, ×6.

Bacteriological Investigations

Ward sisters, house officers, and registrars were encouraged to take swabs and send specimens of sputa, etc., for bacteriological examination wherever there was the least suspicion of sepsis. The specimens were initially plated out on plain blood-agar plates and usually on two or more antibiotic ditch-plates. When staphylococci were isolated they were tested for coagulase by the slide test, and coagulase-positive strains were tested for sensitivity to penicillin, streptomycin, tetracycline, chloramphenicol, erythromycin, novobiocin, and vancomycin. A single colony and a mixed streak from each strain were tested on ditch-plates. The concentrations of antibiotic in the ditch were as follows: penicillin 10 units/ml., chloramphenicol 50 μg./ml., vancomycin 100 μg./ml., all other antibiotics 25 μg./ml. The Oxford staphylococcus was streaked across the centre of each ditch. Strains were recorded as resistant if they grew to the edge of the ditch or right across it, and partially resistant if they grew nearer to the ditch than the Oxford staphylococcus but not to the edge. Except with streptomycin and erythromycin, strains showing partial resistance were uncommon and for the purposes of analysis have been included with resistant strains.

Nasal swabs were also taken from many patients and members of the staff, and these were initially plated on phenolphthalein phosphate nutrient agar (Barber and Kuper, 1951). Subsequent treatment of phosphatase-positive colonies was similar to that described above.

After January 1, 1958, all strains of *Staph. pyogenes* from infective processes and a proportion of those isolated from nasal carriers were bacteriophage-typed by the method of Williams and Rippon (1952).

Incidence and Drug-Resistance of Staphylococcal Infection

The incidence and drug-resistance of staphylococcal infection in the surgical wards between October 1, 1957, and June 30, 1959, have been analysed quarterly and the results are given in Table I and Figs. 1 and 2. Most of the anti-cross-infection measures were introduced before or during the first quarter. The antibiotic policy was introduced at the beginning of the third quarter.

TABLE I.—*Staphylococcal Infection in Surgical Wards, October 1, 1957, to June 30, 1959*

Date	No. of Patients Admitted	Infections									
		Total	Pen. S.*		Pen. R. Tet. S.		Pen. R. Tet. R.		Eryth. R.†	
			No.	%	No.	%	No.	%	No.	%
Oct.–Dec., '57	728	76	9	12	14	18	53	70	8	11
Jan.–Mar., '58	722	83	22	26	19	23	42	51	5	7
Apl.–June, '58	812	74	15	20	18	24	41	56	10	14
July–Sept., '58	783	53	18	34	12	23	23	43	10	19
Oct.–Dec., '58	708	50	19	38	12	24	19	38	10	20
Jan.–Mar., '59	746	58	21	36	12	21	25	43	17‡	29
Apl.–June, '59	740	58	28	48	9	16	21	36	6	10
	5,239	452	132	—	96	—	224	—	66	—

* All but five of these infections were also sensitive to tetracycline and all were sensitive to erythromycin.
† All but one of these infections were also resistant to penicillin and tetracycline.
‡ 11 of these infections were of similar phage type and occurred in a single ward.

All infections have been recorded, however slight, and both wound and chest infections have been included.

It will be seen that during the 21-month period 5,239 patients were admitted to the wards, and 452 (9%) of them had a staphylococcal infection. The total incidence of infections per patient dropped from 10% to 7% between the second and fourth quarters, since when it has remained fairly stable.

The drug-sensitivity of the infection, on the other hand, has changed steadily throughout the period of study. At the beginning of the investigation 70% of the infections were resistant to penicillin and tetracycline

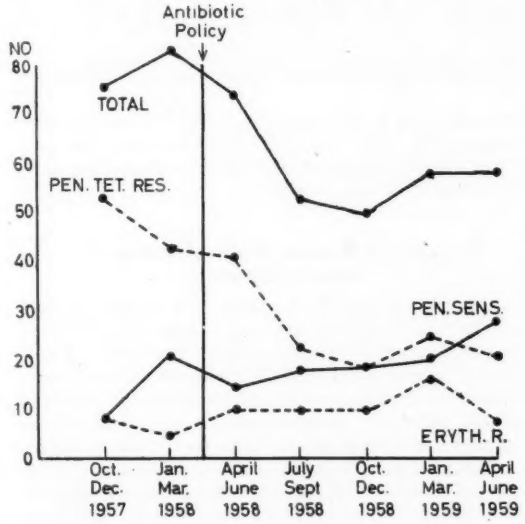

FIG. 1.—Number of staphylococcal infections with various antibiotic-sensitivity patterns.

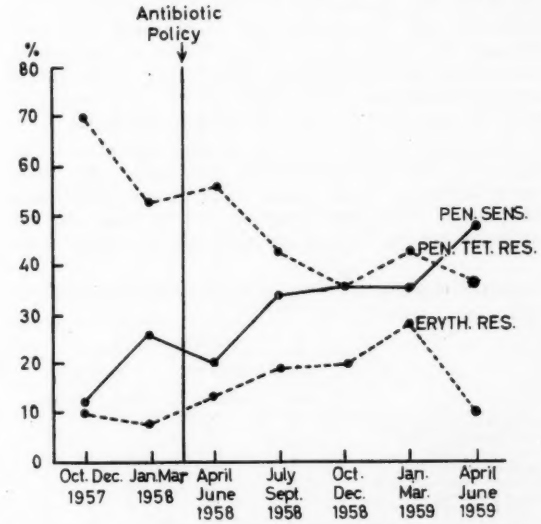

FIG. 2.—Percentage of staphylococcal infections with various antibiotic-sensitivity patterns.

and only 12% were sensitive to all antibiotics tested, including penicillin. In the last quarter the incidence of infection resistant to penicillin and tetracycline had dropped to 36% and that of penicillin-sensitive infection had risen to 48%.

In the last quarter, four of the penicillin-sensitive strains were resistant to tetracycline; only one such strain had been isolated in the previous 18 months. All the penicillin-sensitive strains were also sensitive to streptomycin, erythromycin, and novobiocin, but two, both isolated in the last quarter, were resistant to chloramphenicol.

Most of the penicillin- and tetracycline-resistant infections were also resistant to streptomycin, but 29 of the 224 were sensitive to this antibiotic. As many as 66 of these infections were also resistant to erythromycin. It will be seen from Table I that the erythromycin-resistant infections occurred throughout the period of investigation and that there was no significant change in incidence. The high figure in the sixth quarter, January–March, 1959, was due to an outbreak of infection in which 11 patients in one of the six wards became infected by a single strain of *Staph. pyogenes.*

Chloramphenicol resistance is not recorded in the table, but there were 40 such infections scattered throughout the period of investigation. In 27 instances this was associated with erythromycin resistance, and these 27 infections were in fact resistant to penicillin, streptomycin, tetracycline, chloramphenicol, and erythromycin.

Only one infection resistant to novobiocin was encountered, and none of the infections was resistant to vancomycin.

Generalized and Fatal Infections

Most of the infections recorded were localized to a single site and many were of very little clinical significance. In 49 patients, however, the infection was generalized; 24 of these patients died, and though infection was not usually the sole cause of death it was in every case a major contributory factor. As many as 44 of the generalized infections were resistant to penicillin and tetracycline, and 16 of these were also resistant to erythromycin. All but four of the strains were tested for bacteriophage sensitivity; 11, including six from fatal cases, were phage type 80; the remainder were of various types, all belonging to group III.

Table II shows that 12 of the patients with generalized infection were infected before admission. All these were suffering from renal failure and had been transferred from other hospitals for treatment on the artificial kidney. These patients, all of whom were admitted with infection due to multiple-resistant strains of staphylococci from other hospitals, constituted a major problem in attempting to eradicate such organisms from the hospital being studied. It will also be seen from Table II that the incidence of generalized infection contracted in the hospital has fallen with the fall in the incidence of multiple-resistant infection.

TABLE II.—*Incidence and Mortality of Generalized Staphylococcal Infection*

	Patients Infected			
	Before Admission		In Hospital	
	No.	Deaths	No.	Deaths
October–December, 1957 ..	0	0	14	6
January–March, 1958 ..	2	2	7	5
April–June, 1958	1	1	6	2
July–September, 1958 ..	3	2	3	0
October–December, 1958	2	2	2	2
January–March, 1959 ..	1	0	4	2
April–June, 1959	3	0	1	0
	12	7	37	17

Strains of Staph. pyogenes Responsible for Infection

From January, 1958, the strains of *Staph. pyogenes* isolated from infections in the surgical wards were all tested for sensitivity to bacteriophage. When it was found that two or more infections in a single ward were due to staphylococci with a similar antibiotic-sensitivity pattern and of the same bacteriophage type, it was assumed that a single strain of *Staph. pyogenes* was responsible for all the infections. The wards were taken as separate units because they tended to have staphylococci of different types. On this basis the incidence and drug-resistance of the strains of *Staph. pyogenes* responsible for the infections in the hospital were analysed, and the results are summarized in Table III and Figs. 3 and 4.

It will be seen that following the introduction of the antibiotic policy at the beginning of April, 1958, the percentage of strains sensitive to penicillin rose from 28 to 54. In contrast to this the percentage of strains resistant to penicillin alone fell from 28 to 17; and the percentage of strains resistant to penicillin and tetracycline fell from 44 to 29. The incidence of strains resistant to erythromycin rose to begin with and then fell. This may have been due to the frequent use of chloramphenicol and erythromycin in combination until January, 1959, when attention was drawn to the fact that there was cross-resistance between these two antibiotics (Barber *et al.*, 1958).

TABLE III.—*Strains of Staph. pyogenes Responsible for Infections in Surgical Wards, January,* 1958, *to June,* 1959

Date	Infections								
	Total	Pen. S.*		Pen. R. Tet. S.		Pen. R. Tet. R.		Eryth. R.†	
		No.	%	No.	%	No.	%	No.	%
Jan.–Mar., '58 ..	61	20	33	19	31	22	35	4	7
Apl.–June, '58 ..	50	14	28	14	28	22	44	6	12
July–Sept., '58 ..	43	13	30	11	26	19	44	9	21
Oct.–Dec., '58 ..	35	15	43	10	29	10	29	7	20
Jan.–Mar., '59 ..	38	19	50	10	25	9	24	4	10
Apl.–June, '59 ..	48	26	54	8	17	14	29	4	8

* All but three of these strains were also sensitive to tetracycline.
† All but one of these strains were also resistant to penicillin and tetracycline.

Virulence of Multiple Resistant Strains of Staph. pyogenes

During the course of this study 452 staphylococcal infections were encountered and strains from 369 of these were typed by bacteriophage sensitivity. From this fairly extensive material an attempt has been made to assess the virulence of strains of different antibiotic sensitivity patterns To determine whether certain types of staphylococci were more likely to initiate infection the number of strains (based on bacteriophage typing) of a given antibiotic sensitivity were compared with the number of such infections, and from this the incidence of infection per strain was calculated. The results are given in Table IV, from which it will be seen that with

antibiotic-sensitive strains and strains resistant to penicillin only the incidence was 1.4, whereas with strains resistant to penicillin and tetracycline it was 2.0, and with strains resistant to these two antibiotics and erythromycin it was 3.0. It does not, of course, follow from this that all multiple-resistant strains were more likely to initiate infection than were antibiotic-sensitive staphylococci. Actually the results reflect the fact that a few of the multiple-resistant strains were each responsible for a large number of infections. On the other hand, none of the strains sensitive to all antibiotics tested or resistant to penicillin only was responsible for more than two infections.

TABLE IV.—*Incidence of Infections Caused by Strains of Staph. pyogenes of Different Antibiotic Sensitivities*

Antibiotic Sensitivity of Infecting Strain			No. of Strains	No. of Infections	Incidence of Infections per Strain
Pen.	Tet.	Eryth.			
S	S	S	85	116	1·4
R	S	S	57	82	1·4
R	R	S	59	119	2·0
R	R	R	17	52	3·0

TABLE V.—*Relation of Antibiotic Sensitivity to Incidence of Generalized Infection*

Antibiotic Sensitivity of Infecting Strain			Total No. of Infections	Generalized Infections		
Pen.	Tet.	Eryth.		No.	Percentage of Total	No. of Deaths
S	S	S	132	3	2·3	1
R	S	S	96	2	2·0	0
R	R	S	158	28	17·7	14
R	R	R	66	16	24·2	9

In an attempt to assess the severity of infection caused by strains of different antibiotic-sensitivity pattern, the incidence of generalized infection was studied. From Table V it will be seen that only 3 out of 132 antibiotic-sensitive infections and only 2 out of 96 infections resistant to penicillin only were generalized. Only one patient in these two groups died, and he was 85 years old. On the other hand, as many as 28 of 158 infections resistant to penicillin and tetracycline and 16 out of 66 infections resistant to these two plus erythromycin became generalized, and 23 of these patients died.

Nasal Carriers

Nurses.—A survey of nasal carriers among the entire nursing staff was undertaken six times during the 21 months. The results are given in Table VI. It will be noted that on each occasion approximately half the nurses tested carried *Staph. pyogenes* and that the majority of carriers carried strains resistant to penicillin but sensitive to tetracycline. The percentage of carriers carrying penicillin-sensitive strains increased from 24 to 37 between July and November, 1958, and thereafter remained at the higher level. The incidence of nurses carrying multiple-resistant strains was never high and did not vary significantly during the investigation.

Patients.—In two of the six wards studied nasal swabs were taken from all patients on admission. In all, 1,138 patients were examined and *Staph. pyogenes* was isolated from 344 (30%). The majority (65%) of the carriers carried antibiotic-sensitive strains; 23% carried strains resistant to penicillin only; and strains resistant to penicillin and tetracycline were isolated from 12%. This last figure was unexpectedly high, but was partly accounted for by the fact that more than half the

TABLE VI

Date	No. Examined	No. of Carriers	Antibiotic Sensitivity of Strains		
			Percentage of Carriers		
			Pen. S.	Pen. R. Tet. S.	Pen. R. Tet. R.
October, 1957	446	211	23	69	8
March, 1958 ..	517	240	22	70	6
July, 1958 ..	388	179	24	68	8
November, 1958	450	192	37	59	4
March, 1959 ..	480	235	35	61	4
July, 1959 ..	454	203	38	56	6

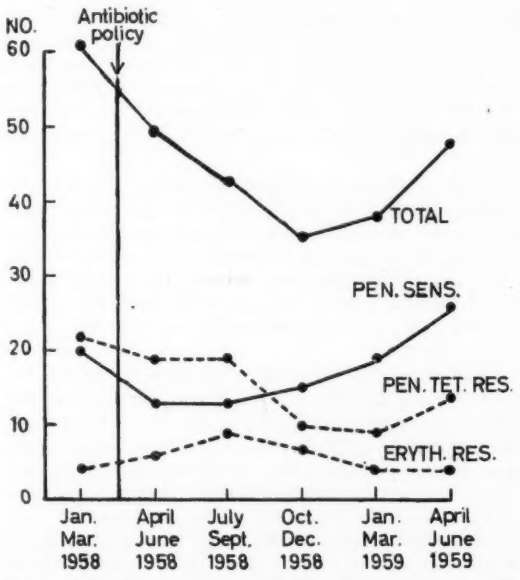

FIG. 3.—Number of strains of *Staph. pyogenes* with various antibiotic-sensitivity patterns.

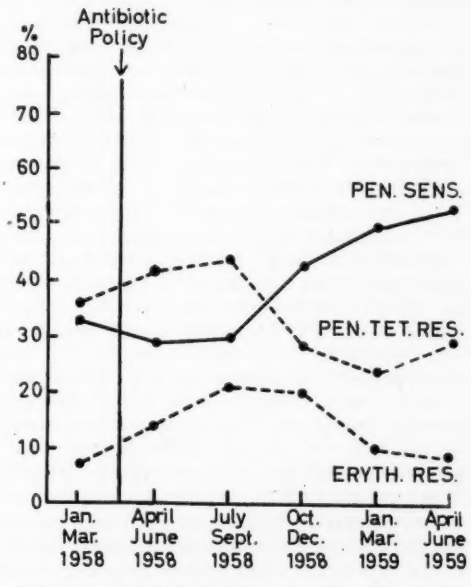

FIG. 4.—Percentage of strains of *Staph. pyogenes* with various antibiotic-sensitivity patterns.

patients who carried multiple-resistant *Staph. pyogenes* in the nose on admission had been transferred from other hospitals for treatment of renal failure.

With 530 patients nasal swabs were taken on admission and on one or more subsequent occasions. In most cases nasal carriage remained constant, but multiple-resistant strains which were isolated from 63 patients after a stay in hospital were not present on admission. Further analysis showed that 41 (12%) of 340 patients with negative swabs on admission picked up multiple-resistant strains, whereas this occurred with only 12 (7%) of 162 patients who on admission carried strains of *Staph. pyogenes* sensitive to all antibiotics or resistant to penicillin only.

Some form of staphylococcal sepsis developed in 116 patients from whom nasal swabs were examined. In 32 cases the strain isolated from the septic process was similar to that isolated from the nose on admission. In 16 cases both strains were antibiotic-sensitive; in 6 both were resistant to penicillin only; and in 10 both were resistant to penicillin and tetracycline. Nasal swabs were taken on more than one occasion from 43 patients who subsequently developed staphylococcal wound infection. As was found in a series recorded by Williams *et al.* (1959), the majority (22 out of 28) of those patients who were carriers at the time of infection had similar strains in nose and wound. But, since 15 of the 43 patients gave consistently negative nasal swabs, it cannot be assumed that nasal infection necessarily precedes or even accompanies wound infection.

Discussion

It is clear from this investigation that the ever-increasing incidence of drug-resistant staphylococcal infection in hospitals can be checked. In the hospital studied, until two years ago, the incidence of staphylococcal infection which was resistant to penicillin and tetracycline was steadily rising, and in October, 1957, the figure had reached 70%, whereas the incidence of infection sensitive to penicillin had fallen to 12%. A year after the introduction of the controlled antibiotic policy the figures were reversed and penicillin-sensitive staphylococcal infections in the hospital were more frequent than infections resistant to penicillin and tetracycline. It is possible that these results might have been even better were it not that with the transfer of patients for treatment on the artificial kidney we were continually being supplied with multiple-resistant staphylococcal infection from hospitals all over England.

To what extent these results are the direct effect of the antibiotic policy is difficult to determine. Undoubtedly the anti-cross-infection measures previously introduced played a part, and were probably responsible for the fall in the total incidence of staphylococcal infection per patient from 10% to 7% between January and July, 1958. The latter figure of 7% cannot be regarded with any satisfaction, but since it includes all forms of sepsis, both of wounds and of chest infections, however insignificant, it compares not unfavourably with the incidence of surgical cross-infection recorded by other workers (Howe, 1954; Jeffrey and Sklaroff, 1958; Shooter *et al.*, 1958).

Analysis, on the basis of bacteriophage typing, of the strains of *Staph. pyogenes* responsible for the infections shows a similar trend towards penicillin sensitivity, which suggests that the actual emergence of drug-resistant staphylococci in the hospital has been checked. Moreover, in the last quarter of the investigation a few individual strains appear to have reverted from drug-resistance to drug-sensitivity. Thus two antibiotic-sensitive strains, of phage type 52A.80 and 83 respectively, were encountered in a ward where strains of similar phage type had previously been resistant to penicillin and tetracycline. Similarly, a strain of phage type 47.53.77 resistant to both these antibiotics appeared to give rise to a mutant sensitive to penicillin but resistant to tetracycline.

It seems likely that these findings are the result of the antibiotic policy, the two most important features of which were limitation in the use of penicillin and double chemotherapy. Reduction in the total amount of penicillin used in the hospital and its total abandonment in four of the six surgical wards probably favoured the natural tendency of penicillinase-producing staphylococci to give rise to penicillin-sensitive mutants. (Barber, 1949; Bondi *et al.*, 1953; Fairbrother *et al.*, 1954).

The introduction of universal double chemotherapy is a potentially dangerous policy, since it entails a considerable increase in the use of each antibiotic and makes it more difficult to keep any in reserve. In the present experiment the consumption of tetracycline antibiotics in the hospital went up; it seems almost certain, therefore, that the policy of always giving a second antibiotic was effective in preventing or at least delaying the emergence of tetracycline-resistant staphylococci. There are, however, other objections to an increase in the use of broad-spectrum antibiotics, and possibly this was one of the reasons for an increase in chest infection due to *Ps. pyocyanea* noted in the second winter of the trial.

Erythromycin and novobiocin were also used more freely than would otherwise have been the case. Staphylococci develop resistance very rapidly to both these antibiotics if administered separately, but so far the combination appears to have been effective in preventing the emergence of resistant strains. Combination of erythromycin with chloramphenicol did not prevent the development of drug-resistance. Though during the course of the investigation the incidence of staphylococci resistant to erythromycin did not significantly increase, unlike that of penicillin- and tetracycline-resistant strains it did not decrease, so that the proportion of multiple-resistant strains which are resistant to erythromycin has considerably risen.

Changes in the nasal carrier state of the nursing staff were less marked, but throughout the investigation it was apparent that the strains of *Staph. pyogenes* carried by the nurses were not the ones responsible for infections in patients. After the introduction of the antibiotic policy, however, there was a small increase in the percentage of nurse carriers who carried penicillin-sensitive strains.

At this stage it is pertinent to ask to what extent this experiment has been of practical value. Seeing that the total incidence of staphylococcal infection per patient remained stationary during the last year of the investigation, how important is the change in drug sensitivity? Provided new antibiotics continue to appear, does drug-resistance matter? In answer to this, evidence has been presented which indicates that some, at any rate, of the multiple-resistant strains of *Staph. pyogenes* in hospital have enhanced capacity both to initiate infection and to cause generalized disease.

It does not, of course, follow from this that drug-resistant strains are always of high virulence. Indeed, in *in vitro* experiments the reverse is usually the case. But in hospitals drug-resistant staphylococci have emerged as the result of the transfer of strains from patient to patient in the presence of antibiotics, and this form of animal passage has inevitably favoured the selection of highly virulent organisms. With the associated elimination of drug-sensitive strains the drug-resistant staphylococci have been left a relatively clear field.

If this is the case, attempts to reverse the process are of considerable importance; but, clearly, a controlled antibiotic policy gives us no respite from fighting cross-infection. Nevertheless, in view of the ubiquity of the staphylococcus and the consequent impossibility of eliminating all potentially pathogenic strains from the hospital environment, it seems reasonable to concentrate on those strains most likely to be dangerous. At present, in most hospitals these appear to be multiple-resistant organisms, usually of phage group III or type 80. It is possible that if we concentrate our attack on these strains we shall favour the selection, in hospitals, of less virulent staphylococci.

Summary

The incidence and drug-resistance of all staphylococcal infections in the surgical wards of a large general hospital have been studied over the period October 1, 1957, to June 30, 1959. In the six months prior to the investigation a number of anti-cross-infection measures were introduced into the hospital, and in April, 1958, a controlled antibiotic policy was put into operation.

During the investigation 5,239 patients were admitted to the wards studied and 452 had a staphylococcal infection. The total incidence per patient of all types of staphylococcal infection fell from 10% to 7% between January and July, 1958, and thereafter remained stationary.

At the beginning of the investigation 70% of the infections were resistant to penicillin and tetracycline and only 12% were sensitive to penicillin. At the end of the investigation 36% of the infections were resistant to penicillin and tetracycline and 48% were sensitive to penicillin. Analysis of the strains of *Staph. pyogenes* (on the basis of phage type) showed a similar trend towards penicillin sensitivity.

Most of the infections were localized and many were very slight, but 49 patients developed generalized infection and 24 of these died; 44 of the generalized infections and 23 of the fatal infections were due to multiple-resistant strains; 12 of these patients had been transferred from other hospitals for treatment of renal failure and were already infected on admission.

It is a pleasure to thank the entire medical, nursing, and administrative staff of the hospital, and especially the sisters of the surgical and penicillin wards, whose magnificent co-operation made this investigation possible. We would particularly like to thank Dr. W. Hayes, who not only played a major part in planning the experiment but was the catalyst who started the reaction.

The antibiotic policy was planned by a joint committee of representatives of the Medical Research Council Antibiotics Clinical Trials Committee and of the staff of Hammersmith Hospital, which consisted of the following people: Professor L. P. Garrod (in the chair), Drs. Mary Barber, A. A. C. Dutton, P. C. Elmes, W. Hayes, P. Hugh-Jones, E. J. L. Lowbury, J. G. Scadding, R. Shackman, and J. P. M. Tizard. We are grateful to Professor L. P. Garrod and Dr. E. J. L. Lowbury for the help they have given us.

Our thanks are also due to Messrs. Eli Lilly for free supplies of erythromycin and vancomycin and to the Glaxo Laboratories Ltd. for free supplies of novobiocin and buffered solution for giving penicillin in cartridge syringes.

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OPEN LUNG BIOPSY FOR DIFFUSE PULMONARY LESIONS

BY

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Diffuse pulmonary lesions have always presented a diagnostic challenge. In spite of intensive investigation, many cases remain obscure until further developments or even necropsy reveal their nature. Various methods have been devised to obtain a portion of lung tissue for histological, bacteriological, or chemical examination. Biopsy by means of a needle, drill, or thoracoscope appears to be inadequate. The only method of obtaining an adequate specimen which is both visibly and palpably diseased is open biopsy. This method was first described by Klassen *et al.* (1949), and further articles have appeared from other centres in the United States. So far no report on this subject has appeared in the British literature. We should therefore like to record the experience of this procedure at the London Chest Hospital during the past five years.

Method

General anaesthesia is employed in all cases. The site of the incision is planned according to the maximal radiological distribution of the disease. In earlier cases a routine thoracotomy incision was used with or without removing the rib. In later cases it was found that a smaller antero-lateral incision, usually about 6–8 in. (15–20 cm.) long, could be employed, with the possibility

of extending it if desirable. The chest is opened through the rib bed without removing the rib. The lung is inspected and palpated, together with hilar and mediastinal nodes. A suitable gland is removed for histological section. A portion of lung approximately 2 by 3 by 5 cm., showing most disease, is excised between two clamps. The lung is sutured in two layers by means of deep mattress and superficial continuous chromic catgut sutures. After insertion of antibiotics the chest incision is closed, leaving an intercostal drain for 24 to 48 hours.

Results

Complications.—There was no operative mortality in this series. In the majority of patients there were no complications, the post-operative course being satisfactory. Only two patients developed minimal pyrexia, and one had a small pleural effusion which needed aspiration three days after removing the tube. In only two cases were the complications more serious. One patient, suffering from a honeycomb lung due to eosinophilic granuloma, developed a spontaneous pneumothorax on the contralateral side on the third post-operative day; although this should be technically regarded as a complication, it is only fair to mention that it may have been a pure coincidence, since spontaneous pneumothorax is quite common in this condition. The other patient developed a subacute intestinal obstruction on the 17th post-operative day which responded well to conservative treatment. Thus the method appears to be safe, complications and operative morbidity being minimal.

Histology.—It will be seen from the Table that in only two cases (Nos. 8 and 13) were the histological findings indefinite, although even in one of these (No. 13) they were sufficient to make the pre-operative diagnosis improbable. In the other 24 a histological diagnosis was made, but in about one-quarter of these the aetiology remained obscure. The number of discrepancies with pre-operative diagnoses and the many interesting features demonstrated will be apparent.

Discussion

Various methods have been suggested and used in an attempt to obtain pulmonary tissue for microscopical and bacteriological examination. It may also be desirable to perform chemical analysis of the tissue obtained.

The simplest method would appear to be needle biopsy. This was first used as long ago as 1883 by Leyden, who performed it in three cases of pneumonia to isolate the invading organisms. Ellis (1947) devised a special biopsy needle with a squared-off cutting edge which is driven into the tissue by means of a dental drilling machine or motor. He applied this technique to the diagnosis of various tumours at different sites with great success and few complications. However, only nine cases of lung biopsy are tabulated, and in these there were two deaths, one immediate and one delayed.

A very full article by Woolf (1954) reviews the literature on the subject and analyses 94 biopsies of his own. He used an ordinary long needle (18 gauge 9 cm. short bevel with stylet), but a Vim–Silverman or similar type of needle has been used by others. Analysis of his results indicates that the procedure is far from being safe, there having been one death and numerous complications (45.8% of cases), though many of these were of a minor nature. Lüdin (1955) reports four cases of severe haemoptysis with one death in a matter of three minutes during this procedure. Dustin (1953), Dutra and Geraci (1954), and Ochsner *et al.* (1947) have reported tumour implantation along the needle track which precluded subsequent surgery in cases of operable

Table of Results

Case	Age	Pre-operative Clinical Diagnosis	Biopsy and Final Diagnosis	Remarks
1	19	Honeycomb lung with diabetes insipidus	Eosinophilic granuloma	Treated by corticotrophin. Process arrested
2	66	Multiple metastases. ? Bronchial primary	Undifferentiated carcinoma with multiple metastases. Primary unknown	Needle biopsy negative
3	26	Hilar adenopathy with collapsed middle lobe	Hodgkin's disease	Bronchoscopic biopsy: "Chronic inflammatory tissue." Treated with nitrogen mustard with improvement. Survived 1 year
4	58	Pulmonary fibrosis. ? Asbestosis	Cystic bronchiolectasis with diffuse leiomyomatosis	
5	38	Pulmonary fibrosis. ? Lymphangitis carcinomatosa	Diffuse interstitial fibrosis. "Hamman-Rich" type	Scalene node negative. Treated with steroids. Complete clearing
6	54	? Sarcoidosis	Sarcoidosis	
7	53	? Lymphosarcoma	1. Undifferentiated carcinoma 2. Mild pneumoconiosis	Scalene node negative. Gastrectomy for lymphosarcoma of stomach 2 years previously
8	46	Pulmonary fibrosis; ? cause	No specific diagnosis	
9	58	? Bronchial carcinoma	Sarcoidosi	Before diagnosis patient had deep x-ray treatment
10	21	Pulmonary tuberculosis	Sarcoidosis	Treated
11	33	Pulmonary fibrosis	Bronchiectasis and bronchiolectasis	
12	43	? Rheumatoid lung	Chronic miliary tuberculosis	Antituberculous treatment
13	40	? Rheumatoid lung	Patchy collapse only. No evidence of collagen disease	
14	51	? Pulmonary tuberculosis	Pneumoconiosis	Metastasis from adenocarcinoma of thyroid, removed 3 years previously, also considered
15	54	Bronchial carcinoma with metastasis	Bronchial carcinoma plus pulmonary fibrosis and bronchiolectasis	Biopsy planned, but lobectomy carried out
16	46	Spontaneous pneumothorax with honeycomb lung	Chronic miliary tuberculosis (healing)	Antituberculous treatment
17	51	? Lymphangitis carcinomatosa	Lymphangitis carcinomatosa	
18	49	Pulmonary fibrosis with bronchiectasis	Sarcoidosis	Treated
19	58	Carcinomatosis right lung	Secondaries from adenocarcinoma. Primary not known	
20	36	Honeycomb lung and diabetes insipidus	Eosinophilic granuloma	
21	54	Bronchial carcinoma. ? Metastases	Disseminated squamous carcinoma with occasional sarcoid nodules. Mediastinal glands: carcinoma and sarcoid	Scalene node: sarcoidosis only
22	64	? Bronchial carcinoma with pneumoconiosis	Tuberculosis with asbestosis	Antituberculous treatment
23	52	Pulmonary tuberculosis with ? bronchial carcinoma	Pulmonary tuberculosis. No carcinoma	Antituberculous treatment. Lobectomy
24	57	Pulmonary fibrosis	Diffuse interstitial fibrosis. "Hamman-Rich" type	
25	12	Cystic honeycomb lung	Histiocytic reticuloendotheliosis	Treated with steroids, with marked improvement
26	62	? Sarcoidosis	Bronchiectasis. Bronchiolectasis	No evidence of sarcoidosis

bronchial carcinoma. One of us (L. J. G.) has performed a number of these biopsies in the past, but has given them up owing to the poor diagnostic yield and the considerable discomfort to the patient, though the number was too small to be of any significance. Since the chance of obtaining an adequate specimen by a random method from a tissue of such loose texture seems remote and the risks are not inconsiderable, it now appears to us to be an unjustifiable procedure.

Heine (1957) describes a method of biopsy through a thoracoscope fitted with a specially designed forceps. One or more portions of the lung "the size of a lentil" are excised, bleeding being controlled by diathermy. A definite diagnosis was reached in 12 of 13 cases, and no serious complication or death occurred. This method would appear to be elegant and simple, but obviously it is impracticable in cases where it is not possible to induce an artificial pneumothorax; in our own cases 9 out of 26 had adhesions in the pleural space. Furthermore, the method seems ill suited for conditions in which the lesions are not absolutely superficial. Mediastinal lesions can be visualized, but the use of a biopsy forceps would appear to be hazardous owing to the danger of damage to vessels at the hilum. Heine himself is far from regarding this as a routine method, and will report further on his experience.

The obvious method of choice is open biopsy. The first series was reported by Klassen *et al.* (1949), and eight years' experience has been gained (Andrews and Klassen, 1957). The original method consisted of a submammary incision 8 to 10 cm. long, using local analgesia with positive-pressure breathing; no suture of intercostal muscles was done and no drainage tube inserted. Presumably local analgesia was found to be unsatisfactory, as general anaesthesia is now used. Following Klassen's article, various large and small series of lung biopsies have appeared in the American literature utilizing or modifying his method (Theodos *et al.*, 1955; Effler *et al.*, 1955; Close, 1955; Bell, 1957). O'Donnell (1955) has recognized that the incision ought to be adequate for removing not only a portion of lung but also the mediastinal nodes if they are involved. Other surgeons (Storey *et al.*, 1953; Harvey *et al.*, 1958) agree that a larger incision, approaching that for a routine exploratory thoracotomy, is desirable. On the other hand, Breckler *et al.* (1957) recommend an incision of 3 to 5 cm.

As mentioned above, the method used at the London Chest Hospital ensures adequate inspection and palpation of the whole lung and removal of the most suitable specimen, together with a mediastinal node.

No procedure can equal open lung biopsy in establishing a definite diagnosis in diffuse pulmonary lesions. The essential problem is when to have recourse to this procedure. All available diagnostic methods should have been fully utilized, depending upon the clinical assessment of the case. Usually at this stage the problem has become limited to a few conditions. It may be argued that scalene-node biopsy should always be preferred to pulmonary biopsy in the first instance. Various authors (Shefts *et al.*, 1953; Longstreth *et al.*, 1957) have reported the results obtained by this procedure as described by Daniels (1949). In only one-third of cases is a positive diagnosis reached even with a very long incision and a dissection carried from the neck into the mediastinum ("cervico-mediastinal" exploration of Harken *et al.*, 1954). Nohl (1958), in a series of 58 cases, obtained 36 positive results out of 41 where the nodes were palpable, and 5 out of 17 where the nodes were impalpable, which is usual in the sort of case we are dealing with here. He points out that the success of the operation depends on the extent of the exposure and the amount of tissue removed, so that it is of necessity a fairly formidable procedure, requiring great skill and care.

Scalene-node biopsy seems to be most useful in cases of neoplastic, infective, or granulomatous pulmonary disease, with maximal correlation in cases of sarcoidosis. However, even the latter diagnosis may be dubious, since a variety of conditions, such as tuberculosis, brucellosis, histoplasmosis, Hodgkin's disease, carcinoma, and berylliosis, may give rise to sarcoid-like lesions in scalene nodes (Jefferson *et al.*, 1954). On the other hand, considering the results of various major reported series of lung biopsy, a specific histological diagnosis appears to have been established in two-thirds of the cases; in the rest no specific lesion is discovered, but the histological end-results—for example, pulmonary fibrosis—can be appreciated in the majority, leaving about 10% where no opinion can be given. It would thus seem that when the scalene nodes are not palpable it is justifiable to go straight on to lung biopsy. It may be contended that this procedure is not without risk, which cannot be denied. In the largest series, that of Andrews and Klassen (1957), out of 119 biopsies there were four deaths, and these occurred in desperately ill patients who were regarded as moribund. In their last 50 there was no death at all. In our own admittedly small series there was no mortality, and morbidity was small. It would seem, therefore, that with proper selection of cases the risk should be minimal.

The establishment of a diagnosis by lung biopsy has more than an academic significance. In other series, as well as in ours, a large number of patients have been proved to be suffering from conditions in which treatment was possible. In this connexion we may quote the following cases.

Illustrative Cases

Case 5. (This case is being more fully reported by Dr. J. Macnamara elsewhere.) The patient was a married woman aged 38 with one year's progressive dyspnoea and three months' complete incapacitation. On examination, markedly cyanosed and dyspnoeic at rest, severe clubbing of fingers, generalized sibilant rhonchi, and crepitations at both bases. *X*-ray film: diffuse infiltration both lungs, more pronounced on the right. Other systems n.a.d. Scalene-node biopsy negative. Differential diagnosis was between a rapidly progressive pulmonary fibrosis and lymphangitis carcinomatosa. Lung biopsy (May 17, 1955) revealed changes of diffuse interstitial fibrosis of "Hamman-Rich" type. Treatment with corticotrophin and subsequently with cortisone was dramatically successful, and the patient is alive and well 3½ years later, having been taken off steroids, with complete clearing of lung fields.

A similar case has recently been reported by Van Slyck (1957). Another case of basal fibrosis of unknown aetiology may be quoted, and illustrates the value of examining a mediastinal node:

Case 18.—This patient, a spinster aged 49, had suffered from swelling and pain in fingers, wrists, and ankles 18 months previously. For one year she had a cough with increasing dyspnoea and recurrent pyrexial episodes. There were persistent fine crepitations at both bases. *X*-ray films: high diaphragms, with fibrosis and patchy atelectasis at both bases; mediastinal glands not enlarged; tomograms showed

fine cystic changes. Bronchogram showed basal bronchiectasis with considerable deformity of the bronchial tree in both lower lobes. Mantoux test negative in all dilutions. Kveim test negative. L.E. cells not found. Cystic bronchiectasis of unknown aetiology; rheumatoid lung and sarcoidosis were considered in differential diagnosis. Lung biopsy (February 11, 1957): A portion of right lower lobe, together with a mediastinal node, was obtained. The lung showed marked fibrosis and bronchiectasis with very scanty scattered sarcoid follicles. The mediastinal node, on the other hand, showed a remarkably active sarcoid process. Treatment with prednisone and antituberculous drugs was started, and has been continued for 18 months. The process appears to have been arrested, and the patient is clinically very much improved.

A further case in which the diagnosis of hilar adenopathy with pulmonary infiltration and a misleading bronchoscopy finding was rapidly solved by a lung biopsy may be quoted:

Case 3.—A young woman aged 26 had erythema nodosum one year before admission. On *x*-ray examination, the left hilar glands were found to be enlarged. While under observation she developed bilateral pain in the chest with wheezing. No other lymph-gland enlargement was noted. *X*-ray films showed gross bilateral hilar adenopathy and a collapsed middle lobe. Mantoux test positive 1:1,000. Sputum repeatedly negative for tubercle bacilli. At bronchoscopy granulomatous areas were seen in the right main bronchus, which on biopsy showed changes of chronic inflammation. A three-months course of streptomycin, P.A.S., and isoniazid was given without any benefit, and the patient continued to lose weight. Thoracotomy (October 12, 1954) revealed hard masses in upper and lower lobes and a collapsed middle lobe, which was resected and biopsy of involved areas of lung and mediastinal gland made. The histology was unequivocally that of Hodgkin's disease. She was given a course of nitrogen mustard, which was repeated on several occasions with much symptomatic relief. She died one year after starting treatment.

The diagnosis of pneumoconiosis is generally a clinical and radiological one, and may be very difficult to substantiate. A number of American authorities lay great stress on the value of biopsy in the establishment of the industrial aetiology of pulmonary changes. They not only examine the histology of the lesion, but may also carry out a microchemical analysis of the inorganic constituents (Effler *et al.*, 1955). This may have a great bearing on the question of compensation, and it may well be that the procedure could be more widely applied in this respect in the problem of pneumoconiosis. Our experience of this type of case is limited to one where the question of asbestosis arose and was disproved.

Case 4.—A woman aged 58 had been working with asbestos fibre for over four years. She had progressive cough and dyspnoea for 3½ years, and radiologically showed a diffuse bilateral pulmonary fibrosis. Sputum was repeatedly negative for tubercle bacilli, fungi, and asbestos bodies. Nevertheless, in view of the long exposure, a diagnosis of asbestosis was considered. Histologically the lung biopsy specimen showed numerous microscopic cysts lined by epithelium of respiratory type. Between these was fibro-muscular tissue and chronic inflammatory cells. A diffuse leiomyomatosis was regarded as the pathological process, in view of the fact that the walls of the alveoli were lined by smooth muscle. No evidence of asbestosis was found.

The condition of "eosinophilic granuloma" of the lung is being increasingly recognized, mainly through lung biopsy (Auld, 1957; Arnett and Schulz, 1957). One of us (Grant and Ginsburg, 1955) reported the first case diagnosed in this country by this method. Since then another case has been similarly diagnosed at the London Chest Hospital. In both these cases there were pulmonary opacities and reticulation, associated with diabetes insipidus. A further case of rapidly progressive honeycombing of the lung had a biopsy very recently, which revealed an interesting example of this group.

Case 25.—A girl aged 12 was seen in 1953 at St. Andrew's Hospital, Bow, because she was not putting on weight. *X*-ray report: "Markings prominent. Nil in lung parenchyma." She remained thin but otherwise well. There was no history of respiratory disorder. Three days before admission she collapsed, became suddenly breathless, and developed productive cough. She failed to improve, was admitted to London Chest Hospital on May 30, 1958, and was found to have a right-sided tension pneumothorax and an enlarged (2 fingerbreadths), firm, and tender spleen. Both lungs showed radiological appearances of gross honeycombing. An intercostal tube was introduced. The lung partially re-expanded, but on the fifth day she developed a left pneumothorax. An intercostal suction tube was inserted on this side as well. The previous radiograph was not available at that time, and it was felt that she was a case of either congenital cystic lung or mucoviscidosis. The latter diagnosis was abandoned on finding trypsin in the stool and a negative sweat test. In view of the failure of the right lung to expand, a parietal pleurectomy was performed through a small submammary incision. The lung appeared grossly cystic, and in view of her serious condition biopsy was not performed. When her condition improved on satisfactory adherence of the right lung, it was decided to do a left lung biopsy combined with a left pleurectomy. At thoracotomy a small portion of lung was taken from the lingula. The section showed histiocytic reticulo-endotheliosis.

Occasionally a lung biopsy is of value in establishing the diagnosis of tuberculosis in cases where the diagnosis may not have been suspected or where it may enter into the differential diagnosis without any confirmatory evidence. Sometimes clinical and radiological findings may be atypical, or a failure to respond to specific antituberculous treatment may lead to the suspicion that tuberculosis is only incidental to some other condition. The following case illustrates this point.

Case 23.—A man aged 52 was admitted to the London Hospital with a diagnosis of granuloma inguinale. There were no chest symptoms or signs, but routine *x*-ray examination revealed a round mass in the right mid-zone which in the lateral view appeared to involve both middle and lower lobes, and to abut upon the hilum. There was also some enlargement of the left hilar nodes and diffuse infiltration in both lower lobes. Sputum was found to contain tubercle bacilli on direct smear. Treatment was therefore started with streptomycin, isoniazid, and P.A.S., and he was transferred to the London Chest Hospital. Treatment was continued for three months without any change in the radiological appearance, although sputum became negative. The possibility of some concomitant condition was considered and bronchoscopy was performed. This showed some pressure on the right lower lobe bronchus, which was deformed and scabbarded. The left lower lobe bronchus also showed considerable narrowing. Sputum was negative for neoplastic cells. It was therefore decided to proceed to lung biopsy. On thoracotomy (May 1, 1958) a large firm mass was found in the fissure, involving the middle lobe and adjacent portion of the right lower lobe. There was also scattered parenchymal disease in both these lobes. A portion was excised and sent for frozen section, which was reported as tuberculous without any evidence of other disease. It seemed likely, therefore, that this was a case of primary tuberculosis in a middle-aged person, and the possibility of a carcinoma or other lesion was excluded.

Another interesting case of tuberculosis with unusual features may be quoted.

Case 16.—A man aged 46 had had shadowing in the right upper lobe since 1947, with local extension in 1949. This was regarded as probably tuberculosis in spite of repeatedly negative sputum examinations. In 1952 a further reactivation in the right upper lobe occurred, and he also developed severe bronchitis followed by a left spontaneous pneumothorax. This proved difficult to re-expand. There were numerous scattered opacities throughout both lung fields, particularly in the upper zones. It was decided to do a lung biopsy and at the same time identify an air leak. On thoracotomy (January 1, 1957) a large leak and small emphysematous bullae were present in the left upper lobe and apex of the left lower lobe. Both lobes were fibrotic, with numerous hard calcified nodules scattered throughout. Microscopical examination of a biopsy specimen showed lesions strongly suggestive of calcifying chronic miliary tuberculosis. He was put on antituberculous drugs for the first time.

From these illustrative cases it is apparent that much can be expected in the way of providing a definitive diagnosis and a rational basis for therapy, and even where therapy is not possible a radical change in prognostic outlook may result.

As regards the academic value of such a procedure there can be no question that much hitherto inaccessible information may be derived from it, since it enables the pathological histology of various disease processes to be studied during their active phases. It is interesting to note that one observer (Close, 1955) did not hesitate to do two successive biopsies on the same patient in order to observe the effect of treatment. It appears to us that there is a field for a great increase in the use of this valuable procedure, from all points of view, and it is also possible that it should be considered earlier as a diagnostic measure, since it could be carried out in a fitter patient and might be even better tolerated, thus leading to the earlier institution of treatment.

Summary

A series of 26 cases of lung biopsies by thoracotomy is presented. Complications were minimal.

The importance of securing an adequate specimen, including an affected mediastinal lymph node, is emphasized.

The advantages of open lung biopsy over other biopsy procedures are stressed.

The method appeared to be of great value in establishing a histological diagnosis in diffuse pulmonary lesions and rational treatment for various conditions. The histological diagnosis was obtained in 24 out of 26 cases.

We wish to thank the consultant staff of the London Chest Hospital for allowing us to review and quote their cases, and Dr. Hilton Lewinsohn for his helpful criticism.

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ABO BLOOD GROUPS AND SECRETOR CHARACTER IN RHEUMATIC CARDITIS

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Glynn *et al.* (1956) emphasized that there must be important host factors in rheumatic fever because, though the disease usually follows a streptococcal throat infection, only a small proportion of cases of streptococcal tonsillitis do, in fact, develop the complication. They pointed out that one important variation in the environment of the streptococcus depends on the blood-group secretor status of the host, and this idea led them to investigate the secretor character in patients with rheumatic fever. In 460 schoolchildren, who were used as controls, they estimated an incidence of 22.6% non-secretors of ABH from the results of an anti-Le^a serum and saliva test (most individuals who are non-secretors of ABH secrete large amounts of Le^a), whereas among 450 children with rheumatic fever the estimated non-secretor figure was 28.7% and the difference was significant at the 5% level.

The same authors have recently published further data (Glynn *et al.*, 1959). Using the same salivary anti-Le^a technique, they found a Le^a-positive incidence of 21.2% in 1,129 healthy schoolchildren as compared with 27.5% in 611 cases of rheumatic fever (significant at the 1% level). Similar results were obtained with *Ulex* extract, which tests directly for secretor status by showing the presence or absence of H-substance, this being present in the saliva and other body fluids in secretors of any of the ABO blood-groups. By the *Ulex* method, Glynn *et al.* (1959) found that 22.9% of 669 healthy schoolchildren were non-secretors and the comparable figure in 553 rheumatic fever cases was 28.9% (significant at the 2% level).

Glynn *et al.* (1956) gave details of the ABO blood-group distribution among patients and controls, and,

though not commented on, the former appear to be rather high in B and AB at the expense of group O. In their second paper they did not report the ABO blood groups of their patients, but they have kindly sent us their latest figures and allowed us to use them in our analyses. Again there is no significant difference between patients and controls, but, taken at their face value, their disease group still appears to be rather low in group O.

Material and Methods

We became interested in the problem after reading the paper by Glynn *et al.* (1956). Since then we have tested 228 Merseyside patients known to be suffering from established mitral stenosis, the purpose being to find out whether a high non-secretor rate was also present in this post-rheumatic condition. For the same purpose we also collected a series of 35 children who had been affected with rheumatic carditis.

Our control for the blood-group data is the group of individuals in Table I of Clarke *et al.* (1955) plus those in Table III of Clarke *et al.* (1959). The control for the secretor comparisons is from Table I of Clarke *et al.* (1959). This has been used rather than the data in Table III of the same paper, as the numbers are larger and the secretor character is independent of the ABO blood groups.

The salivary secretor character was assessed by means of the agglutination-inhibition technique, and for patients of blood group O we used an extract of *Ulex* (for details see Clarke *et al.*, 1956). The ABO blood-grouping had usually been done by the thoracic surgical unit at Broadgreen Hospital, Liverpool, from which most of the cases of mitral stenosis were obtained, and sometimes this finding was used. Most of the groupings were, however, done by us using precipitin tubes and anti-A and anti-B sera. In a certain number we also Lewis-grouped the red cells.

Results

Table I gives our basic data, the cases being subdivided to show secretor status, ABO blood group, and sex. We also differentiated between those who gave a previous history of rheumatic fever or chorea and those whose case-notes contained no record of rheumatic fever. All the 35 children in whom the carditis was or had been active are included with the mitral stenosis patients who are known to have a history of rheumatic fever.

There is no heterogeneity in the ABO blood group and secretor/non-secretor frequencies, either between males and females with a history of rheumatic fever, or between males and females with no history of rheumatic fever. There is also no heterogeneity between these two disease groups with the sexes combined in respect of blood-group and secretor frequencies. Consequently in the final comparisons with controls (Tables II and III), the sexes and the disease groups have been combined.

TABLE I.—*Basic Data of a Series of 263 Cases of Rheumatic Carditis*

Blood Group	Total Series		History of Rheumatic Fever or Chorea		No Record of Rheumatic Fever	
	Sec.	Non-sec.	Sec.	Non-sec.	Sec.	Non-sec.
Males (64)						
O	20	8	14	2	6	6
A	18	6	10	2	8	4
B	5	4	3	3	2	1
AB	3	—	2	—	1	—
	46	18	29	7	17	11
Females (199)						
O	58	19	26	9	32	10
A	62	30	25	15	37	15
B	21	6	10	1	11	5
AB	3	—	1	—	2	—
	144	55	62	25	82	30
Total	190	73	91	32	99	41

ABO Blood Groups.—Table II shows the numbers and percentages of the different blood groups in our disease and control series. The Taplow rheumatic fever series in the same table is from a personal communication from Dr. L. E. Glynn, and its control is from Table IV of Glynn *et al.* (1956). It will be seen that there is the same trend in the result of the two investigations—namely, a lower percentage of group O in the disease series than in the controls. We have therefore analysed the data comparing the incidence of the disease in group O people and those not group O, using the method of Woolf (1955). The statistical analysis shows that on combining the results from the two investigations there is no heterogeneity between them and there is a significantly increased incidence of the disease in those who are not group O.

TABLE II.—*Numbers and Percentages of the Different Blood Groups in Disease and Control Series*

Blood Group	Liverpool Data				Taplow Data			
	Rheumatic Carditis		Control		Rheumatic Fever		Control	
	No.	%	No.	%	No.	%	No.	%
O	105	39·9	7,842	48·8	255	41·9	6,775	45·0
A	116	44·1	6,294	39·2	256	42·0	6,456	42·9
B	36	13·7	1,519	9·5	64	10·5	1,311	8·7
AB	6	2·3	402	2·5	34	5·6	504	3·4
Total	263	100·0	16,057	100·0	609	100·0	15,046	100·0

Statistical Analysis

	Relative Incidence of Disease in Not-O People	d. of f. = 1	P	95% Fiducial Limits
Liverpool	1·44	8·15	<0·01	
Taplow	1·14	2·36	>0·1	
Combined	1·22	8·15	<0·01	1·40–1·06
Heterogeneity	—	2·36	>0·1	

TABLE III.—*Numbers and Percentages of Non-secretors in Disease and Control Series*

	Liverpool Data				Taplow Data			
	263 Rheumatic Carditis		851 Controls		553 Rheumatic Fever		669 Controls	
	No.	%	No.	%	No.	%	No.	%
Non-sec.	73	27·8	207	24·3	160	28·9	153	22·9

Statistical Analysis

	Relative Incidence of Disease in Non-secretors	d. of f. = 1	P	95% Fiducial Limits
Liverpool	1·20	1·26	>0·2	
Taplow	1·37	5·82	<0·02	
Combined	1·30	6·63	<0·02	1·58–1·06
Heterogeneity	—	0·45	>0·3	

Secretor Character.—Table III shows the numbers and the percentages of non-secretors in the disease and control series from Liverpool and Taplow. The Taplow rheumatic fever series and its control consist of the ulex-

tested individuals from Table IV of Glynn *et al.* (1959). The Liverpool series is not significantly different from its control with regard to the incidence of non-secretors but does show a non-significant excess of them. The statistical analysis shows that on combining the results from the two investigations there is no heterogeneity between them, and there is a significantly increased incidence of the disease in those who are non-secretors.

Discussion

It will be seen that in the Liverpool results there is a significant association between the disease and the ABO blood groups, whereas the excess of non-secretors, though present, is not significant. The converse is the case with the Taplow investigation; but there is no heterogeneity between the two series, and the combined result is significant for both characters. Even so, the levels of significance do not approach those needed before such an association can be regarded as well founded, because of the difficulty of getting adequate control series. Thus the need for large numbers in this field of research is again emphasized, and it is to be hoped that the data presented in this paper will be augmented by workers elsewhere. Should this result in convincing proof of these associations with rheumatic fever, it would be the first demonstration of an association between blood groups and a bacterial disease since the finding of Struthers (1951) in pneumonia in infancy. In addition, further data would enable a definite conclusion to be drawn about an interesting feature (though one not significant with present numbers) of both the Liverpool and Taplow series. This is that the percentage of non-secretors is particularly high in the patients of groups A and B (Liverpool group O=25.7% and group A=31%; Taplow, group O=25.5% and group A=30.1%).

If the reactions of the haemolytic streptococcus are affected materially by the secretor status of the host, it might be possible to demonstrate differences in virulence or growth rate depending on the amount of water-soluble blood-group substances present in the culture media. This investigation is now being carried out. Finally, it would be interesting to know whether or not the blood-group and secretor differences present in rheumatic fever are also present in series of patients with uncomplicated streptococcal throat infections and in those who develop acute nephritis.

Summary

Data are presented of a series of 263 Liverpool patients suffering from rheumatic carditis. They show a significant reduction in the incidence of blood group O and a non-significant increase in non-secretors compared with controls. There is no heterogeneity between our results and those from Taplow (Glynn, 1959, personal communication) in where there is a significant excess of non-secretors and a non-significant deficiency of group O. On combining the results of the two investigations there is a significantly increased incidence of the disease both in those who are not group O and in those who are non-secretors.

The levels of significance are suggestive of there being a relationship between rheumatic fever and the ABO blood-group antigens, but the collection of further data is indicated, not only of rheumatic fever but also of uncomplicated streptococcal throat infections and acute nephritis.

We are indebted to Dr. L. E. Glynn for supplying us with the blood-group data of his series and for his permission to use them in this paper. We are also grateful to the consultants of the thoracic surgical unit at Broadgreen Hospital, to Dr. E. N. Chamberlain, and to Dr. S. Cope for giving us access to their patients; and to Dr. J. Wyn Edwards, who collected blood and saliva from some patients in the earlier part of the investigation. Our thanks are due to our senior technician, Mr. W. T. A. Donohoe, for carrying out much of the serological work, and to our research assistant, Miss Sheila M. Manning, who has been invaluable in collecting the greater part of the material and in carrying out all the secretarial work. The research has been made possible with the aid of grants from the Medical Research Committee of the United Liverpool Hospitals under the chairmanship of Lord Cohen of Birkenhead, the Nuffield Foundation, and the Medical Research Council.

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PRACTICAL DIETS FOR LOWERING SERUM LIPIDS

A LONG-TERM STUDY ON OUT-PATIENTS WITH ISCHAEMIC HEART DISEASE

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The effects of dietary fats on blood lipids have aroused considerable interest in recent years in view of the probable relationship to coronary heart disease. Morrison (1955), in a controlled study of patients with myocardial infarction, reported that life could be prolonged by taking a low-fat diet; the serum cholesterol, total lipids, and neutral fat were all reduced. Lyon *et al.* (1956), with a larger series, showed similar effects on survival accompanied by a lowering of low-density lipoproteins. A fall in blood lipids can also be produced by the isocaloric replacement of saturated fats by unsaturated oils (Kinsell *et al.*, 1952; Ahrens *et al.*, 1954, 1957; Bronte-Stewart *et al.*, 1956), but there have been few studies showing that a regimen containing unsaturated fats can be used by patients in their home surroundings and may be effective over long periods (Groen *et al.*, 1952; Malmros and Wigand, 1957).

For the past 18 months we have been studying the long-term effects of various treatments in men with ischaemic heart disease. Data are now available showing the effect on the blood lipids, and in this paper we report the relation of a low-fat diet and of an unsaturated-fat diet to lipid levels. It is too early for comment to be made on any effect on the disease process.

Procedure

The patients were first classified into three diagnostic groups: (*a*) Myocardial infarction, with abnormal Q waves, or a history of pain for more than one hour at rest with major electrocardiographic changes. (*b*) Angina of effort with electrocardiographic changes at rest or on exercise, but no abnormal Q waves. (*c*) Angina of effort without electrocardiographic changes.

They were further subdivided according to age, and then randomly allocated to five treatment groups: (1) Phenindione to give a single-stage prothrombin time between two and three times normal. (2) Phenindione 1 mg. as control. (3) Unsaturated-fat diet. (4) Unsaturated-fat diet with a lower phenindione dose to give a single-stage prothrombin time of one and a half times normal. (5) Low-fat diet.

For analysing the lipid changes, groups 1 and 2 are referred to as the "anticoagulant group," groups 3 and 4 as the "unsaturated-fat diet," and group 5 as the "low-fat diet"; this is justifiable, since the anticoagulants did not lower blood lipids. The anticoagulant group served as a control for the dietary groups. Dietary histories were taken before and during treatment.

Methods

20 ml. of blood was taken at three-monthly intervals, when the patients attended after their usual breakfast. The following lipid estimations were then made: (*a*) Total cholesterol (Abell *et al.*, 1952). (*b*) Low-density lipoprotein; a modified ultracentrifugal method (Lindgren and Gofman, 1957) using refractive index increment 1.51×10^{-3} per g. per 100 ml. (Hanig and Shainoff, 1956). The following estimations were made after the study had progressed several months, but no pre-treatment data are available. (*c*) Total cholesterol in low-density fraction. (*d*) Calculations of concentration of molecules Sf 0-12 and Sf 12-400, using *b* and *c* in regression equations (Lindgren and Gofman, 1957).

Low-fat Diet.—This diet contained no dairy produce except skimmed milk, and one egg or ¾ oz. (21 g.) of cheese a day. Lean meat and fish were each allowed once a day; fruit, vegetables, and other non-fatty foods were allowed in unlimited quantity. This diet stipulated 20 g. of fat, but in practice 20–30 g. was eaten daily.

UNSATURATED-FAT DIET

	FOODS NOT ALLOWED	FOODS ALLOWED
FATS	Butter, margarine, dripping, lard, and *all other fats and oils*. See footnote	*Only* the oil permitted.* It is important to use 3–4 oz. (8 tablespoonfuls) daily, i.e., in frying (not to be reused for frying) and in place of other fats in cooking, e.g., for cakes and pastries etc.
EGGS	Egg yolk	Egg white—e.g., (1) for meringues (stiffly beaten), puddings, and cakes; (2) for binding in cakes and batters where whole eggs are normally used.
MILK	Whole milk, condensed or evaporated milk, powdered whole milk, and cream	Skim-milk. Condensed skim-milk (tinned). Powdered skim-milk
CHEESE	Cheese made from whole milk, or containing cream	Cottage or curd cheese made from skim-milk (home-made by letting skim-milk sour and hanging curds in a muslin bag)
MEAT		All lean meat now permitted
FISH		All fish, fresh or tinned, or shellfish
FRUIT AND VEGETABLES		All fruits and vegetables
SOUPS	Made with meat stock, whole milk, or fat	Vegetable soup, cream soup made with skim-milk and oil. Fish soup
MISCELLANEOUS SUGARY AND STARCHY FOODS	Ice cream, chocolates, toffee, fudge	Nuts, sugar, sweets, jams, honey, bread, Matzos, cereals, cakes, and biscuits made *without* egg yolks, butter, cream, or cooking fat. N.B.—These sugary and starchy foods should be cut down if weight needs reducing
3 MONTHS LATER		¼lb. (113 g.) of a relatively unsaturated margarine per week

*Unsaturated oils permitted: soya, maize, safflower, sunflower.

Unsaturated-fat Diet.—All dairy produce, except skimmed milk, was eliminated from a meat-free diet. Fish and vegetables were allowed without restriction, and the unsaturated fat was supplied in the form of soya oil (90 ml. daily). The soya oil had an iodine value between 130 and 135.

After six months restrictions were relaxed and lean meat was allowed. Later, up to ¼ lb. (113 g.) weekly of a relatively unsaturated margarine was also permitted.

Results

Table I shows that in both dietary groups there was a marked drop in the blood-level of cholesterol and low-density lipoproteins; this reduction has persisted ($P<0.01$). The unsaturated-fat diet produced the greatest mean reduction, while patients receiving only anticoagulants showed no significant change.

During treatment it was noted (Table II) that concentrations of Sf 0–12 lipoproteins and of Sf 12–400 lipoproteins were significantly lower on both diets, as compared with the anticoagulant group ($P<0.01$). Comparison of the effects of the diets, moreover, showed that while there was a similar reduction of Sf 0–12 lipoproteins, a significantly greater drop of Sf 12–400

TABLE I.—*Mean Serum Lipids (mg./100 ml. ±1 Standard Deviation) in Different Treatment Groups*

Treatment Group	No. of Patients	Serum Cholesterol		Low-density Lipoprotein		Duration of Treatment in months
		Before Treatment	During Treatment	Before Treatment	During Treatment	
Anticoagulants	23	288±34	294±38	902±156	931±161	12·5±6·4
Unsaturated-fat diet	23	287±54	210±33	838±141	624±113	13·7±3·3
Low-fat diet	12	296±43	219±34	849±180	680±150	13·5±5·1
Standard error for blind duplicates		8·3 mg.		22·6 mg.		

lipoproteins occurred in those patients taking the unsaturated-fat diet ($P<0.01$).

Table III refers to the composition of the diets, and Table IV compares the weight changes. Patients in the anticoagulant group gained slightly, those on the unsaturated-fat diet lost slightly, and those on the low-fat diet lost considerably. It seems reasonable to explain this by caloric differences.

TABLE II.—*Mean Estimated Concentration of Molecules Sf 0–12 and Sf 12–400 (mg./100 ml. ± S.D.) During Different Treatments*

Treatment Group	Sf 0–12	Sf 12–400
Anticoagulants	464 ± 63·8	422 ± 108·7
Unsaturated-fat diet	345 ± 54	263 ± 84
Low-fat diet	359 ± 19·8	318 ± 103·2

TABLE III.—*Composition of Diets Taken During Treatment Calculated from Histories (Protein Values Obtained by Difference)*

Treatment Group	Calories per day	Carbohydrates (g./day)	Fat (g./day)	Protein (g./day)
Anticoagulants	2,040	235	80	95
Unsaturated-fat diet	1,875	240	75	60
Low-fat diet	1,425	240	25	60

TABLE IV.—*Mean Weight*

Treatment Group	Before Treatment		During Treatment	
	lb.	kg.	lb.	kg.
Anticoagulants	164 ± 19·7	74·4 ± 8·9	168 ± 18·1	76·2 ± 8·2
Unsaturated-fat diet	160 ± 9·5	72·6 ± 4·3	156 ± 11·5	70·8 ± 5·2
Low-fat diet	159 ± 15·2	72·1 ± 6·9	147 ± 13·1	66·7 ± 5·9

Discussion

These findings agree with previous reports on the efficacy of fat restriction and of the substitution of unsaturated for saturated fats; further, they show that a lipid-lowering diet is a feasible and attractive proposition.

Nichols *et al.* (1956) found in isocaloric experiments that the serum level of Sf 0–12 lipoproteins (rich in cholesterol esters) is established by saturated fats, while that of Sf 12–400 lipoproteins (rich in neutral fat) is determined by the carbohydrate content of a diet. Walker *et al.* (1957) have shown that the Sf 12–400 level is also influenced by the calorie balance. This implies that Sf 0–12 lipoprotein, and therefore the serum cholesterol level, can be lowered by removing saturated fat from the diet. This can be done isocalorically by replacing the saturated fat with carbohydrate, when the level of Sf 12–400 lipoprotein and neutral fat will rise. Alternatively, unsaturated fats which do not raise this lipid class can be given. In isocaloric experiments the unsaturated fat diet is the more effective (Nichols *et al.*, 1956; Ahrens *et al.*, 1957). The drop in cholesterol and Sf 0–12 lipoprotein in our patients is explained by the removal of saturated fats from their diets. The drop in Sf 12–400 lipoprotein levels in patients on the low-fat diet can be explained by the considerable loss of weight. The still greater reduction of this class of lipid in patients on the unsaturated-fat diet demands a different explanation: it is suggested that unsaturated fats can lower the level of Sf 12–400 lipoprotein directly. It should be stressed, however, that too much ought not to be read into dietary histories, and this explanation must therefore remain open to question.

Throughout, our patients have co-operated well. Those on the unsaturated-fat diet find it much more palatable, and have eaten enough to maintain weight. When the patient has shown that he has co-operated effectively he is allowed a ¼ lb. (113 g.) of a relatively unsaturated margarine weekly, and as it is no longer necessary to exclude lean meat the menu is made more attractive, so that such a diet presents no hardship to a patient living at home.

These diets do not necessarily influence the prognosis of ischaemic heart disease, and much more extensive trials must be carried out before a definite conclusion can be drawn about ultimate benefits. Indeed, it is of interest in this respect that Oliver and Boyd (1959) have presented data showing that the lowering of serum cholesterol and lipoprotein levels by oestrogens produces no change in mortality.

It is our intention merely to indicate that a satisfactory and practical way to lower serum lipids, as a group, is by an unsaturated-fat diet.

Summary

Serum cholesterol and low-density lipoproteins have been effectively reduced by dietary means in out-patients with ischaemic heart disease over a period of more than one year.

The unsaturated-fat diet is more efficient than the low-fat diet; it achieves, without loss of weight, lower levels of serum cholesterol, low-density lipoprotein, and Sf 0–12 and Sf 12–400 lipoproteins, the last significantly so.

The unsaturated-fat diet, being less monotonous, is better tolerated. The diet sheet now supplied to our patients is included.

This communication is part of a long-term study made possible by a generous grant from the Margarine Manufacturers Association. We also thank Messrs. Van Den Berghs and Jurgens Limited for the donation of scientific apparatus. The work is also supported by a research grant from the St. George's Hospital Endowment Fund. We are grateful to Professor T. Crawford and Professor A. C. Dornhorst for help with the manuscript, and particularly to Miss M. E. Carey, chief dietitian, St. George's Hospital.

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CLINICAL TRIAL OF TWO CORONARY VASODILATOR DRUGS

BY

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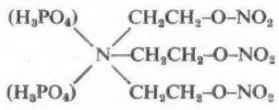
Glyceryl trinitrate is now widely used for the rapid relief of acute episodes of cardiac pain. It is not of value in preventing pain except when taken immediately before effort. The search continues for a long-acting nitrate drug which, if taken regularly throughout the day, would prevent cardiac pain.

Two such drugs have been prepared and used in trials recently. A sustained-action nitroglycerin (" nitroglyn ") was found by Huppert and Boyd (1955) to be moderately effective, while Fuller and Kassel (1955) and Heller (1956) reported good results in using triethanolamine trinitrate biphosphate (" metamine "). However, Russek *et al.* (1955a, 1955b) and Riseman *et al.* (1958) found that these two drugs were ineffective, and other clinical reports have produced further conflicting evidence.

We have been able to study the effect of these drugs on the frequency and duration of episodes of cardiac pain in 30 patients with ischaemic heart disease. This paper presents the results of our double-blind trial.

Pharmacology

Triethanolamine trinitrate biphosphate (T.T.B.) has the chemical formula:



The work of Junkmann (1940) and other European pharmacologists on the biological properties of T.T.B. has been reviewed by Fuller and Kassel (1955). It has been shown to be an effective coronary vasodilator which compares favourably with nitroglycerin (Melville and Lu, 1951), though T.T.B. has a lesser but a definite effect on the systemic blood-pressure and cardiac output than nitroglycerin (Merlen, 1951).

The mechanism of the vasodilator action is not certain. Melville and Lu (1951) showed that there is little *in vitro* nitrate-to-nitrite conversion, and claimed that the action of T.T.B. does not depend upon hydrolysis of nitrate.

Nitroglyn.—This is a porous plastic tablet impregnated with nitroglycerin so that there is a slow release and sustained action of the nitroglycerin. Gorlin *et al.* (1959) have studied the mode of action of nitroglycerin, and conclude that its primary effect is to increase the oxygen consumption of heart muscle and secondarily to cause coronary vasodilatation.

Patients and Method

Thirty patients, seven of whom were female, were studied. All had cardiac pain on effort and an electrocardiogram showing evidence of ischaemic heart disease. Twenty-two had had at least one myocardial infarction, and in seven this had occurred within six months of the trial. No patient was in heart failure during the trial, but three had been in left ventricular failure in the past. A Wassermann test had been done on 18 patients, and was negative in all. Three patients had mild essential hypertension, and a fourth was taking rauwolfia. Sixteen patients were taking phenindione at the time of the trial.

Three types of tablets were used, identical in shape and colour: T.T.B. 2 mg., nitroglyn 2.5 mg., and a placebo. They were coded A, B, or C, and were given in a sequence of any one of six possible combinations over a period of three weeks. For example, some patients received A the first week, B the second week, and C the third week; others had tablets in sequence B, C, A; others had C, A, B, and so on.

The sequence of tablets was varied to avoid two possible causes of error in the results. (1) If the tablets had been given in one sequence only to our seven patients with a recent myocardial infarction, the last tablet in the sequence might have seemed the most effective, as such patients often have progressively fewer attacks of cardiac pain. (2) The action of one drug might be potentiated by another when taken next in sequence, and so appear more effective.

Tablets were given on the first four days only of each week, as daily activity would tend to be more constant over this period than any other. No tablets were given on the last three days of each week, lest the action of any one drug should continue beyond the test period. Each patient took two tablets four times daily, before meals and before going to bed.

Each patient was given three cards, one for each week, and was asked to record daily the time of onset of each attack of cardiac pain, its duration in minutes, and the total number of glyceryl trinitrate tablets taken. (Patients were allowed to continue to take glyceryl trinitrate 1/100 gr. (0.65 mg.) as needed.)

Results

Those patients taking the placebo tablets had significantly more attacks ($P>0.01$) lasting from two to four minutes than patients taking either of the two trial drugs (Table I). The number of attacks of cardiac pain lasting one half to one minute and two to four minutes together, however, was about the same for each of the three tablets. Similarly the total number of attacks of all durations was the same whether the trial or the placebo tablets were given.

We concluded that, though T.T.B. and nitroglyn did not reduce the number of attacks of cardiac pain, they did benefit patients who had frequent short attacks by shortening them further. Attacks of pain lasting longer than four minutes, however, were not affected.

TABLE I.—*Number of Attacks of Cardiac Pain of Different Durations in 30 Patients*

Duration of Attack	Nitroglyn	T.T.B.	Placebo
½–1 minute	74	88	44
2–4 minutes	83	81	119
5–15 ,, ...	82	80	79
Over 15 ,, ...	14	7	11
	253	256	253

The 16 patients treated with phenindione and either T.T.B., nitroglyn, or placebo had fewer attacks than those who were given the trial drugs and placebo alone (Table II). The difference is highly significant ($P>0.01$).

Finally, the 30 patients were classified according to their grade of cardiac pain (Table III). These patients had the same number of attacks when given the two drugs or placebo, irrespective of their capacity for effort; T.T.B. and nitroglyn did not benefit any one grade more than another.

The total number of glyceryl trinitrate tablets needed by patients while treated with T.T.B., nitroglyn, or placebo were very similar (T.T.B. 319, nitroglyn 298, placebo 305) and substantiated the fact that neither drug in the dose given reduced the severity of the attacks of cardiac pain.

TABLE II.—*Effect of Phenindione on Number of Attacks of Cardiac Pain of Different Durations in 30 Patients*

Duration of Attack	Nitroglyn		T.T.B.		Placebo	
	+	−	+	−	+	−
1–1 minute ..	21	53	34	54	17	27
2–4 minutes ..	31	52	49	32	48	71
5–15 ,, ..	41	41	28	52	28	51
Over 15 ,, ..	6	8	3	4	8	3
	99	154	114	142	101	152

+ = With phenindione (16 patients). − = Without phenindione (14 patients).

TABLE III.—*Number of Attacks Occurring in 30 Patients with Different Grades of Cardiac Pain**

Grade	No. of Patients	Nitroglyn	T.T.B.	Placebo
I ..	7	45	45	38
II ..	6	55	50	56
III ..	11	126	120	134
V ..	1	3	6	6
VI ..	5	24	35	19
		253	256	253

* No patients in grade IV.

Grades of cardiac pain: I, Pain produced only on hurrying or walking up hills. II, Pain produced when walking at an ordinary speed on the level. III, Pain that occurs even when a person walks slowly. IV, Total incapacity so that cardiac pain occurs on the slightest provocation and nearly always at rest also. V, Acute or subacute coronary insufficiency with depressed S–T segments at rest and repeated relatively long-lasting attacks of rest pain without infarction. VI, Cardiac infarction.

Side-effects were very few. Two patients complained of gastro-intestinal symptoms while taking the placebo tablet, and one patient developed nausea and dizziness from nitroglyn.

Discussion

When used to measure the effect of coronary vasodilator drugs on cardiac pain, subjective evidence might reasonably seem to yield less dependable results than the Master two-step effort test. This test is not without risk, however, and was thought unjustifiable in this study. The total numbers of episodes of cardiac pain are so strikingly similar for each tablet (253 for nitroglyn, 256 for T.T.B., and 253 for the placebo) that it can be strongly argued that the witness for each patient was reliable enough to make valid our frequency-duration method of assessing results of treatment.

Our results show that there is a small but significant effect upon the duration of shorter episodes (two to four minutes) of cardiac pain during the treatment with nitroglyn or T.T.B., but that there is no effect upon longer episodes (over four minutes) or upon the total number for any one drug. It is possible that larger doses of both drugs would have been more effective. However, Riseman *et al.* (1958) found that 18 mg. of T.T.B. daily was ineffective, and Russek *et al.* (1955a) found that a single dose of 6 mg. of T.T.B. did not improve the effort tolerance in the Master two-step test. The absence of side-effects from T.T.B. suggests that the dose was too low (Friend *et al.*, 1954), or that it is a feeble vasodilator when given by mouth (Riseman *et al.*, 1958). We have not been able to confirm the substantial claims made for T.T.B. (Dailheu-Geoffroy, 1951; David and Rouleau, 1957).

A dose of two 2.5-mg. tablets of nitroglyn is probably not enough. Russek *et al.* (1955a) found that only 50% of their patients were any better when taking twice this dose, and Riseman *et al.* (1958) gave twice to four times the suggested dose (up to four 2.5-mg. tablets four times daily) before 57% of 14 patients were moderately or markedly improved.

The considerable improvement in patients who were being treated with phenindione and the trial drugs compared with those who were not receiving anti-coagulants is very interesting. Dicoumarol has been shown to have a coronary vasodilator effect (Gilbert and Nalefski, 1949), and Graham *et al.* (1951) reported that heparin therapy coincided with a decrease in frequency of attacks of cardiac pain in 55 out of 59 patients. This latter effect, however, was shown to coincide with a change of lipoprotein pattern. The mechanism of pain relief during phenindione treatment is not known.

It is clear that T.T.B. and nitroglyn have only a small effect in patients with uncomplicated ischaemic heart disease. They may be useful drugs, however, to reduce the length of shorter episodes of cardiac pain if taken in doses at least as large as those used in this trial.

Summary and Conclusions

Two long-acting coronary vasodilators have been given to 30 patients with ischaemic heart disease to assess their effect upon the number and duration of attacks of cardiac pain. Sixteen of the patients were known to be taking phenindione.

Triethanolamine trinitrate biphosphate 4 mg. four times daily, nitroglyn 5 mg. four times daily, and a placebo were given in random sequence for three separate four-day periods, using the double-blind technique.

T.T.B. and nitroglyn reduced the duration of attacks lasting two to four minutes, but had no effect on those lasting longer. Neither drug reduced the total number of attacks.

Patients treated with phenindione and either T.T.B., nitroglyn, or placebo tablets had significantly fewer attacks of cardiac pain than those who were not receiving anticoagulant.

Dr. Paul Wood kindly suggested this trial. We thank the physicians of the National Heart Hospital for permission to study their patients. We also thank the many other people in the hospital who helped us, and Dr. P. Crosland-Taylor and Dr. F. O'Grady, of the Middlesex Hospital, for invaluable work with the statistics. Mr. T. Mowat, of Medo-Chemicals Ltd., kindly supplied the triethanolamine

trinitrate biphosphate and placebo tablets, and the nitroglyn was supplied by the Key Corporation, Miami, Florida.

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A METASTASIZING CARCINOID TUMOUR WITH UNUSUAL FEATURES

BY

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Carcinoid tumours arise from specialized epithelial cells in the gastro-intestinal tract known as Kultschitzky cells, which in recent years have been shown to secrete 5-hydroxytryptamine. The presence of excessive quantities of this substance in the blood of patients with metastasizing carcinoid tumours may produce a characteristic clinical syndrome of cutaneous flushing, diarrhoea, asthma, and right-sided valvular disease of the heart. Not all metastasizing tumours produce this syndrome, and the following case, which shows many unusual features, was originally diagnosed 22 years ago as an inoperable carcinoma of the pancreas.

Clinical Record

A retired civil servant aged 62 had his first attack of jaundice in 1927 at the age of 30; this was transient and was attributed to infective hepatitis.

In 1937 jaundice recurred, but on this occasion it steadily deepened. The liver was enlarged five fingerbreadths below the costal margin and the gall-bladder was palpable. A laparotomy by Mr. R. M. Vick at St. Bartholomew's Hospital showed a mass 1½ by 2 in. (3.8 by 5 cm.) in the head of the pancreas and a liver studded with secondary deposits. A palliative cholecystogastrostomy was performed. No biopsy was taken. After the operation the jaundice cleared, but the colour returned to the stools for a short time only. Subsequently these became loose, pale, and offensive, five or six a day, but his main complaint over the next few years was of recurrent attacks of severe abdominal pain probably pancreatic in origin.

In 1944 he developed oedema due to hypoproteinaemia (serum albumin 2.6 g./100 ml.). Treatment with a high-protein low-fat diet and intravenous infusions of plasma resulted in a rise in serum albumin, disappearance of the oedema, and some improvement in the steatorrhoea. Shortly after discharge from hospital he had a further attack of jaundice, thought to be a serum hepatitis.

In 1952 he became jaundiced again, the serum bilirubin rising over three weeks to 32.5 mg./100 ml. A laparotomy was performed by Professor I. Aird at Hammersmith Hospital, the operation note being as follows: "The liver was grossly enlarged, with about a dozen hard white nodules characteristic of a carcinoma deposit. In the head of the pancreas and related to the termination of the common bile duct there was a stony-hard tumour encircling not only the common duct but also the lower part of the portal vein. The remainder of the pancreas presented to palpation and vision the characteristic appearances of chronic pancreatic obstruction. The common bile duct was grossly distended and there was only a tiny fistulous opening between the gall-bladder and duodenum. This was closed and a Roux-en-y choledochojejunostomy performed. Biopsies were taken from the liver and from the pancreatic mass through the lumen of the common bile duct. The appearances of the liver were exactly those described at the first operation."

Histological report (Dr. E. D. Williams): "Naked-eye examination of the liver biopsy showed one main nodule of tumour tissue (0.8 cm. diameter) and two smaller ones. On microscopy these consisted of clumps and strands of closely packed polygonal cells embedded in a meshwork of loose fibrous tissue. In some areas there was a tendency to an acinar structure and in one part there were well-formed tubules. The tumour nuclei were remarkably uniform in size and shape, and only occasional mitoses were seen. The clear vacuolated cytoplasm contained a few granules which did not stain with the Masson silver technique or with the diazo reagent. The pancreatic biopsy was badly distorted and consisted mainly of dense fibrous tissue, but in one area at the edge of the specimen there was similar tumour tissue to that described above. Despite the absence of specific granules, the histological appearances were typical of a carcinoid tumour."

The patient made a good recovery from the operation, though the steatorrhoea and recurrent bouts of abdominal pain continued. He also complained of nocturnal polyuria and cramp in the hands and feet, suggestive of tetany, but never had any attacks of flushing or cyanosis.

Results of Examination

In 1958 he was readmitted for further assessment. He was thin with a dry, scaly skin and slight, pitting oedema of the ankles. Trousseau and Chvostek signs were negative. The liver edge was hard but regular, and was palpable three fingerbreadths below the costal margin. There was no splenomegaly or ascites. The cardiovascular system was normal apart from a soft systolic murmur at the apex.

Investigations.—Haemoglobin, 12.9 g./100 ml.; M.C.H.C., 30%; white-cell count, 6,000, with a normal differential; sternal marrow, normal. Serum electrolytes: sodium 130, potassium 4.1, chloride 99, bicarbonate 25, calcium 4.0, phosphate 1.9 mEq/l. Serum proteins: albumin 3.6 g., globulin 3.0 g./100 ml.; serum amylase 170 units. 5-hydroxyindole acetic acid excretion, 10.5, 10.7, and 9.2 mg. per 24 hours (normal range 3–13 mg.). Liver-function tests: serum bilirubin, 0.3 mg./100 ml.; thymol turbidity, 0 unit; alkaline phosphatase, 21 units; serum G.O.T. 25 units/ml., serum G.P.T. 25 units/ml. Bromsulphthalein test, less than 10% dye retention at 30 minutes. Prothrombin time, 14.5 seconds (normal 10–11 seconds). Liver biopsy, only normal tissue obtained. Intestinal absorption tests: stool examination, numerous undigested meat fibres; no fat-forming organisms on culture. Glucose tolerance, normal. Starch tolerance, abnormal; no significant rise in blood sugar after 50 g. of starch by mouth. Fat balance (75 g. intake): first three days, average daily excretion 64.7 g.; second three days, average daily excretion 38 g. Radioactive fat studies (labelled with

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iodine-131): impaired triolein, normal oleic acid absorption. Radioactive vitamin B_{12} absorption impaired. Folic acid clearance and absorption tests showed folic acid deficiency with impaired intestinal absorption.

A straight *x*-ray film of the abdomen showed pancreatic calculi, and a barium follow-through examination revealed a dilated small intestine consistent with steatorrhoea.

Treatment

The patient was given large doses of pancreatin, but, though the stools were thought to be less fatty, there was no change in fat absorption as measured by radioactive triolein. On the supposition that an abnormal bacterial flora might be contributing to the steatorrhoea a course of antibiotics (chlortetracycline, chloramphenicol, and succinylsulphathiazole consecutively, each for five days) was given but with no improvement either clinically or in fat excretion. He was discharged on pancreatin and a low-fat diet. Since then there has been no change in his condition. Random fat analyses done as an out-patient have shown a fat excretion varying between 70 and 90 g. daily.

Discussion

Kultschitzky cells have been described in the efferent ducts of the pancreas, and Willis (1940), in reporting two cases of metastasizing carcinoid tumour of the small intestine, postulated that some or all of the deposits in the pancreas might have been multiple primary formations. No proved case of a primary carcinoid tumour of the pancreas has, however, been reported, and it is much more likely in the present case that the tumour arose in the duodenum. This is a rare site for carcinoid tumours; they usually arise in the first part, within 1 in. (2.5 cm.) of the pylorus, but a few in the region of the ampulla of Vater have been reported. These, as in the present case, presented with obstructive jaundice (Brentano, 1920; Warren and Coyle, 1951; Mrazek *et al.*, 1953), but in one of them (Brunschwig and Childs, 1939) the common bile duct opened separately in the duodenum below the ampulla of Vater and the presenting feature was a severe pancreatic steatorrhoea.

The term "carcinoid" was applied to these tumours in the belief that they were benign despite the histological resemblance to carcinoma. Subsequent experience has shown this to be untrue and they are now regarded as slowly growing malignant tumours and will probably all metastasize eventually. The commonly occurring tumours in the appendix tend to be diagnosed early and consequently are removed before they have time to metastasize, whereas in the small intestine they can persist for much longer before producing symptoms. Even when metastases are present the prognosis may be measured in years. In occasional cases prolonged survival may occur, the longest reported being that of a patient who died of an unassociated lobar pneumonia 20 years after a laparotomy had shown extensive retroperitoneal metastases (Mallory, 1940). At necropsy these metastases did not appear to have increased in size.

One of the most remarkable features of the case here recorded was the lack of any signs or symptoms of the carcinoid syndrome such as flushing, asthma, or right heart lesions, despite the presence of hepatic metastases for 22 years. Diarrhoea, oedema, and hypoproteinaemia may also occur in this syndrome, but in the present case they were clearly due to the severe pancreatic deficiency. Nevertheless, the impairment of absorption of both vitamin B_{12} and folic acid suggests some additional functional or structural lesion of the intestinal wall which might be related to the carcinoid tumour. Occasionally, however, malabsorption of both these substances occurs in pure pancreatic steatorrhoea (McIntyre *et al.*, 1956; Chanarin *et al.*, 1958). It is now believed that 5-hydroxytryptamine is chiefly destroyed in the liver (Thorson, 1956; McKusick, 1956), hence the importance of hepatic metastases in the pathogenesis of the flushing syndrome, for when this substance is produced in the liver it will escape destruction and reach the systemic circulation in high concentrations. In support of this hypothesis Thorson (1958) found that in 40 cases of metastasizing carcinoid tumours without the flushing syndrome all the deposits were drained by the portal system, whereas at least 11 out of 12 cases with flushing had deposits in the liver, ovary, or abdominal wall, which drained direct to the inferior vena cava without passing through the liver parenchyma.

Not only were there no signs of the carcinoid syndrome but there was also no biochemical evidence of increased 5-hydroxytryptamine formation such as an increased excretion of 5-hydroxyindole acetic acid—its principal breakdown product—in the urine. This is even more surprising, for Thorson (1958) found that, apart from a doubtful exception reported by Knauff (1956), all the carcinoid tumours of the small intestine with metastases that had been investigated biochemically had shown evidence of increased 5-hydroxytryptamine formation. Not all these cases showed clinical signs of the carcinoid syndrome, and there appears to be a wide individual variation in the body's ability to deal with and respond to excess 5-hydroxytryptamine. There may be a considerable daily variation in the output of 5-hydroxytryptamine acetic acid (Hanson and Serin, 1955; Snow *et al.*, 1955), and occasionally it may even drop to normal, but in the present case it was within the normal range on three widely separate occasions.

The question then arises whether the lack of activity might be correlated with the absence of specific granules on histological examination. Although the majority of tumours associated with the flushing syndrome are reported as argentaffin-positive there are several (Snow *et al.*, 1955; Duncan *et al.*, 1955) in which cytoplasmic granules could not be demonstrated. Thorson (1958) described two cases, both with advanced signs of a functioning tumour, one of which was strongly argentaffin, whereas the other with exactly the same technique was negative, though both tumours contained large quantities of 5-hydroxytryptamine. Occasionally one portion of a tumour may be negative and another strongly positive, and metastases from argentaffin primary tumours are not always positive.

It is noteworthy that carcinoid tumours in other sites, such as the rectum and bronchus, rarely show granules, and Warner and Southren (1958) described two cases of metastasizing bronchial tumours with the flushing syndrome in which no granules could be demonstrated. The granules are now believed to be artifacts produced by the interaction of 5-hydroxytryptamine and the formol-saline used in fixation. For their demonstration not only must this be used but also the material must be fixed soon after removal from the body. Nevertheless, these considerations do not always explain the variable staining properties of carcinoid cells, and it is possible that the agranular tumours arise from the pre-enterochrome cells described by Erspamer (1939) as

the non-granular precursors of the normal Kultschitsky cells in the intestinal crypts.

Summary

An unusual case of a metastasizing carcinoid tumour is described in which, despite the presence of hepatic metastases for 22 years, there was no clinical or biochemical evidence of increased 5-hydroxytryptamine formation. The site of origin was probably in the second part of the duodenum, and the main clinical features were obstructive jaundice and severe pancreatic steatorrhoea.

I thank Mr. R. M. Vick, Dr. C. M. Fletcher, and Professor I. Aird, who in turn have looked after this patient, for permission to quote from their original notes. I am indebted to Dr. C. C. Booth and Dr. I. Chanarin for the studies on vitamin B_{12} and folic acid, and to Dr. E. D. Williams for the histological report.

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VALUE OF PLASMA PEPSINOGEN ESTIMATION

BY

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It has long been recognized that there is some relationship, but certainly not a direct one, between the rate of secretion of gastric pepsin and the excretion in the urine of uropepsinogen. It is also known that patients with peptic ulceration have as a group a higher uropepsinogen than non-ulcer patients, and that the amount excreted is reasonably constant for any one individual; nor does this amount fluctuate as does gastric pepsin under nervous, psychic, and chemical stimuli. Clinical interest in uropepsin excretion has declined because of the considerable overlap in values, derived from normals and patients with peptic ulceration, and because of the considerable practical difficulties that attend any measurement made on 24-hour collections of urine.

It is generally agreed that there is a need for some test to supplement tubal aspiration analysis or ion-exchange resins as indices of gastric function or gastric cell mass. To this end we have used the level of plasma pepsinogen in a single sample of 5 ml. of venous blood. Mirsky *et al.* (1952a) demonstrated that its mean coefficient of variation in any one individual from hour to hour in any day is 8% (range 2–22%), and that the daily fluctuation over a month was 12–18%. Hoar and Browning (1956), who repeated Mirsky's work, also found a reasonably constant plasma level with a coefficient of variation of 4%. We ourselves substantially agree with these findings, and have noted, with previous authors, that the plasma level is little affected by food, exercise, or mental stress. Accordingly we consider it permissible for clinical purposes to examine a single plasma sample which will, within fairly narrow limits, characterize an individual's plasma pepsinogen level.

Method

The method used is a modification of that described by Mirsky *et al.* (1952b). A 2.5-ml. sample of plasma from an oxalated specimen of the patient's blood is added to 10 ml. of human plasma substrate at *p*H 2 (1 ml. contains 20 mg. of dehydrated plasma), the *p*H of the resultant mixture being readjusted to *p*H 2 with 2 N HCl, and the volume made up to 15 ml. with distilled water and mixed thoroughly. An aliquot (6 ml.) of this mixture is incubated in a water-bath at 37° C. for 24 hours, after which time the reaction is stopped by the addition of 10 ml. of 4% trichloracetic acid. After filtration of the protein precipitate the concentration of acid-soluble "tyrosine-like" substances is determined by Folin and Ciocalteau's method (A). In this method 2 ml. of filtrate and 3 ml. of the colour reagent are added to 20 ml. of 0.25 N NaOH, and the mixture is examined in a photoelectric absorptiometer ("Spekker") at room temperature. By the similar analysis of 6 ml. of the mixture added to 10 ml. of trichloracetic acid the concentration of chromogenic substances present in the mixture without previous incubation is determined (B): subtraction gives the amount of chromogenic substances produced during incubation. As chromogenic substances also appear after prolonged incubation of the plasma substrate itself, two controls (C and D), each of plasma substrate (4 ml.) and water (2 ml.), are treated similarly to the plasma-digestion mixtures, A and B. From these readings the amount of chromogenic substance (largely tyrosine) liberated by the proteolytic actions of 1 ml. of plasma can be calculated, as in the following example:

		Optical Density
Plasma substrate+water, incubated	=	40 (C)
Plasma substrate+water, non-incubated	=	30 (D)
∴ colour produced by incubation of substrate	=	10
Plasma-digestion mixture incubated	=	100 (A)
Plasma-digestion mixture, non-incubated	=	45 (B)
∴ colour produced by incubation of plasma-digestion mixture	=	55
But 10 units of this is due to incubation of plasma alone		
∴ colour produced by the proteolytic action of plasma	=	45

In this paper, plasma pepsinogen is reported in terms of the amount of tyrosine liberated by 1 ml. of plasma—that is, micrograms (or units) of tyrosine released from 80 mg. of dehydrated plasma at 37° C. in 24 hours by

1 ml. of plasma. Plasma, when not estimated for pepsinogen immediately, was stored frozen at −10° C. Frozen storage up to a period of three weeks did not affect the proteolytic activity.

Results

Single or repeated plasma pepsinogen estimations were made of 74 normal (non-ulcer) subjects, of whom 36 were females (aged 20–60) and 38 were males (aged 21–64). The overall mean plasma pepsinogen was 79 units (range 30–160): females, mean 78 (range 30–160); males, mean 80 (range 50–160). Repeated estimations on any one individual were constantly within 10% of the initially obtained figure. Fluctuation did not seem to bear any relationship to sleeping, waking, exercise, food, or emotional state; for example, there was no immediate pre-operative rise.

Mirsky *et al.* (1952a) demonstrated that plasma activity increases until the age of 20 and remains fairly constant thereafter. As in our results, they noted the tendency for values to be slightly higher in men than in women.

Functional Dyspepsia.—The diagnosis of functional dyspepsia has been given to a group of patients who may have the following characteristics: (*a*) Dyspepsia, not amounting to severe pain, with inconstant relationship to meals and which does not awaken the patient at night. (*b*) Discomfort not relieved by alkalis or food. (*c*) Associated anxiety state or nervous traits: appetite usually poor. Repeated negative barium studies. (*d*) No remission of symptoms such as characterize peptic ulceration. Fifty-two patients, in whom the diagnosis of functional dyspepsia had been made in a gastro-enterological clinic, were reviewed: approximately two-thirds of these were females. The mean plasma pepsinogen estimation was 89 (range 30–180). In 2 of the 52 patients the plasma pepsinogen was consistently above the highest range of "normal" values. This is not surprising in such a clinical group, as quite possibly some atypical peptic ulcers are included.

Duodenal Ulcer.—In 28 adult patients (predominantly male) with chronic duodenal ulceration the mean value was 200 units (range 100–550): only nine patients had values below 160, the lowest being 100. No evidence was obtained that the plasma pepsinogen level fell in patients medically treated, and in no patient was activity or quiescence of the ulcer pain associated with changes in plasma level. About 10% of acute perforations in duodenal ulcers requiring surgical treatment occur without previous indigestion or pain. As Illingworth (1953) remarks, they occur as "a bolt from the blue." Many such patients later develop further ulcer symptomatology; a smaller number escape with the single dramatic episode. Nine such patients who had perforated "acute" duodenal ulcers from 3 to 10 years previously and who had suffered no further significant dyspepsia were reviewed. Their mean figure was 190 (range 50–250), and five of them had levels of 160 or higher. This suggests that patients with a "single episode" duodenal ulcer have similar pepsinogen characteristics to those with chronic duodenal ulceration.

Results of Operation.—In 39 patients submitted to a Polya type of partial gastrectomy (two-thirds resection) for chronic duodenal ulceration the mean post-operative plasma reading was 80 (range 20–160). At the outset of this study it was questioned whether after operation lower levels of plasma pepsinogen might be found in patients showing post-operative loss of weight and nutritional disability: no such correlation was found. Among six cases of duodenal ulceration submitted to gastro-enterostomy and vagotomy the post-operative plasma reading was 160 (or higher) in four, perhaps suggesting that vagotomy does not greatly reduce plasma pepsinogen levels: Gray *et al.* (1954) have noted that uropepsinogen excretion was not grossly affected by antrectomy and vagotomy. In four patients with proved anastomotic ulcer following partial gastrectomy the plasma pepsinogen was still 120, 100, 160, and 100 respectively. These figures imply that a high pre-operative pepsinogen should possibly encourage a more radical resection at the time of partial gastrectomy. Concomitantly, a high post-operative pepsinogen is certainly associated with an increased risk of anastomotic ulceration.

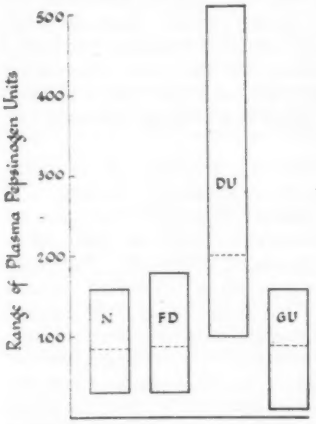
Chronic Gastric Ulcer.—In a group of 13 adult patients suffering from a radiologically demonstrated gastric ulcer the mean plasma pepsinogen level was 90 units. This is approximately half of the mean associated with chronic duodenal ulceration. The range in the gastric ulcer group was a wide one, with a maximal figure of 164 units. A follow-up of 21 patients in whom a limited Polya partial gastrectomy (a half-resection) had been performed some years previously for chronic gastric ulceration revealed a mean figure for plasma pepsinogen of 60 (range 0–120): this is a lower reading than that which followed a similar but more radical partial gastrectomy for chronic duodenal ulceration.

Discussion

It is well established that gastric juice which contains acid also contains pepsin. Though there is no direct correlation between the parameters, Farmer *et al.* (1953) reported that, as a group, patients with duodenal ulcer have a higher concentration of gastric pepsin than normals, in addition to a larger volume and greater acidity of gastric contents. It is also reasonably well established that uropepsin excretion reflects the activity of peptic glands of the stomach. This again is not a direct relationship, for, as Broh-Kahn *et al.* (1948) remarked, food stimulates gastric acid and pepsin secretions but has little or no effect on the rate of excretion of uropepsin. Similarly, Hirschowitz *et al.* (1955) demonstrated the considerable variation between the levels of gastric pepsin and uropepsin in a patient who developed an exacerbation of a duodenal ulcer while on corticotrophin. Again vagotomy, antrectomy, or the administration of anticholinergic drugs do not significantly reduce uropepsin excretion.

The relative immobility of the uropepsin level to a wide variety of stimuli which are known to affect gastric secretion is also found with the plasma estimation. In addition to the stimuli already mentioned, Spiro *et al.* (1955) considered there to be little variation after insulin or histamine administration and noted that plasma pepsinogen does not help in the differentiation of benign and malignant stomach ulcers. Certainly in four patients with very advanced gastric carcinomata studied by us the levels were 90, 250, 110, and 100. By contrast, in four patients submitted to total gastrectomy, plasma pepsinogen was not detected on repeated post-operative examination. Poliner and Spiro (1958) have reported increased plasma pepsinogen in association with achlorhydria in some cases of atrophic gastritis.

As with reported studies on uropepsin, the plasma levels of pepsinogen in non-ulcer and duodenal ulcer patients have considerable overlap, though the great majority of the latter have readings over 160 units, while normal patients and those with functional dyspepsia or chronic gastric ulceration are below this arbitrary level (see Chart). In addition, the mean figure for the duodenal ulcer group is more than twice that of the normals and of the patients with functional dyspepsias or chronic gastric ulceration. That there is such overlap is not surprising, as the digestive activity of the juice is only one component in ulcer formation: high levels of pepsinogen can only express a liability to the development of ulceration (Weiner *et al.*, 1957).



Range and mean values of plasma pepsinogen in normal subjects (N), and patients with functional dyspepsia (F.D.), duodenal ulcer (D.U.), and gastric ulcer (G.U.). The dotted line indicates the mean figures.

It is apparent that neither plasma nor uropepsin levels can be considered to be correlated directly with the amount and concentration of gastric pepsin, and that these assays are possibly better regarded as being related to the chief-cell mass of the stomach rather than to chief-cell activity. This is suggested by both the lack of lability in these assays and the findings that gastro-enterostomy and vagotomy do not grossly influence plasma pepsinogen level, that two-thirds partial gastrectomy reduces it by approximately a half, and that total gastrectomy eliminates the enzyme entirely. Tongen (1950) contended on histological evidence that there is correlation between gastric acidity and parietal cell concentrations in human stomachs, and similar studies may be able to show a similar relationship between plasma pepsinogen and chief cells.

The plasma technique has the advantages of requiring a single blood sample and being unaffected by the common day-to-day stimuli. Even with its obvious limitations it probably has a useful place in the diagnosis of duodenal ulceration and of anastomotic ulcers. Further investigation is required to assess its helpfulness in differentiating haematemesis due to duodenal ulceration from that of portal hypertension. It may possibly serve as a guide to the amount of stomach resection to be undertaken for duodenal ulceration.

Summary

The plasma pepsinogen has been estimated in 246 patients.

The maximal and mean figures for patients with chronic duodenal ulceration are much higher than those found in normals and in patients who have gastric ulceration or functional dyspepsia.

It is suggested that a single plasma estimation reflects the gastric chief-cell mass; the consequent effect of a partial gastrectomy is to reduce the pre-operative level by about a half.

It is suggested that a pre-operative level of plasma pepsinogen may give some indication of the amount of stomach to be resected for chronic peptic ulceration.

We wish to acknowledge help from Miss Sheila Winn; also the kind assistance of Dr. H. P. Brody and a succession of house-surgeons who furnished plasma samples.

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RECOVERY FROM BUTHALITONE ANAESTHESIA

A METHOD OF ASSESSMENT

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The ideal anaesthetic for use in an out-patient department is one which, among other things, permits a rapid return to normal consciousness. Buthalitone sodium has been claimed to possess this property as well as various other advantages over existing agents (Weese and Koss, 1954; Nobes, 1955a, 1955b; Ruddell, 1955). The present investigation was designed to compare buthalitone sodium with thiopentone sodium, using a new technique to measure the rate of recovery.

Method

Thirty-seven unselected out-patients attending for orthopaedic manipulation or minor surgery were given alternately thiopentone and buthalitone. The dosage was such that comparable anaesthesia was achieved with each drug: a 70-kg. man receiving 600 mg. of thiopentone or 1,250 mg. of buthalitone (8.6 mg./kg. or 17.85 mg./kg.). These figures agree closely with others that have been published (Orkin *et al.*, 1958; Henderson and Mackett, 1958). The patients either had premedication of atropine 1/100 gr. (0.6 mg.) or nothing.

When quietly resting before anaesthesia patients were each given a board and tracing paper. The purpose of

*The clinical work was carried out at the Middlesex Hospital, London. Present appointment: Anaesthetist to the North Middlesex Hospital, Edmonton.

the experiment was explained and the patients were asked to trace a straight line, sine wave, and circle already drawn on the board. Below these they were asked to sign their name and make a free drawing of a house (Fig. A). This procedure was repeated as soon as consciousness was regained, and again on two further occasions at approximately 30-minute intervals (Figs. B, C, and D); 37 sets of "drawings" were collected in this way. The drawings were assessed by an observer who did not know which anaesthetic agent was used for each patient (and who was indeed entirely unconnected with the hospital). The method was as follows. Each of the three post-anaesthetic drawings (the order of which was unknown to the assessor) was marked, using the pre-anaesthetic drawing as a baseline, 4 marks being allotted to each of the five items. Thus, if the patient's drawing was as good after the anaesthetic as before it he received a mark of 20 for that drawing.

When the marks were compared with the times (recorded from the beginning of the anaesthetic) it was seen that they reflected a steady return to normal consciousness; there was no instance of a lower mark following a higher one. This in itself provided evidence of the objectivity of the method.

Analysis of Results

For each patient we had a set of three markings varying from 0 to 20, relating to three periods of time following the anaesthetic. These times were not the same for each patient. The first drawing was made only when the patient was sufficiently recovered; and even after that no strict time-table was practicable. To simplify the analysis, therefore, we calculated for each patient the score at 30 minutes and 60 minutes, using linear interpolation (and rounding to the nearest whole number). For example, a patient scoring 12 marks at 15 minutes and 16 at 35 minutes was given an estimated score of 15 at 30 minutes. Patients who had not recovered consciousness scored zero.

The Table gives the distribution of markings at 30 and 60 minutes, together with the medians (calculation of the means might be misleading owing to the relatively large number of zero marks). At 30 minutes the advantage lay slightly with the buthalitone patients, the median being 13.1 compared with 9.8. However, this difference is one that might easily be due to chance, as can be seen from the similarity of the distributions.* By 60 minutes there was even less difference between the two groups of patients.

Numbers of Patients With Various Scores at 30 and 60 Minutes

Score	30 Minutes		60 Minutes	
	Thiopentone	Buthalitone	Thiopentone	Buthalitone
0	7	6	3	1
1	—	—	—	—
2	—	1	—	—
3–6	—	—	—	—
7	—	—	—	1
8	—	—	—	1
9	2	—	—	—
10	1	—	—	1
11	1	1	1	1
12	—	1	1	—
13	—	2	2	—
14	1	2	2	2
15	1	1	—	1
16	2	1	2	2
17	—	3	1	1
18	3	1	5	5
19	—	—	1	2
20	—	—	—	1
Total	18	19	18	19
Median*	9·8	13·1	15·2	16·4

* Based on exact scores.

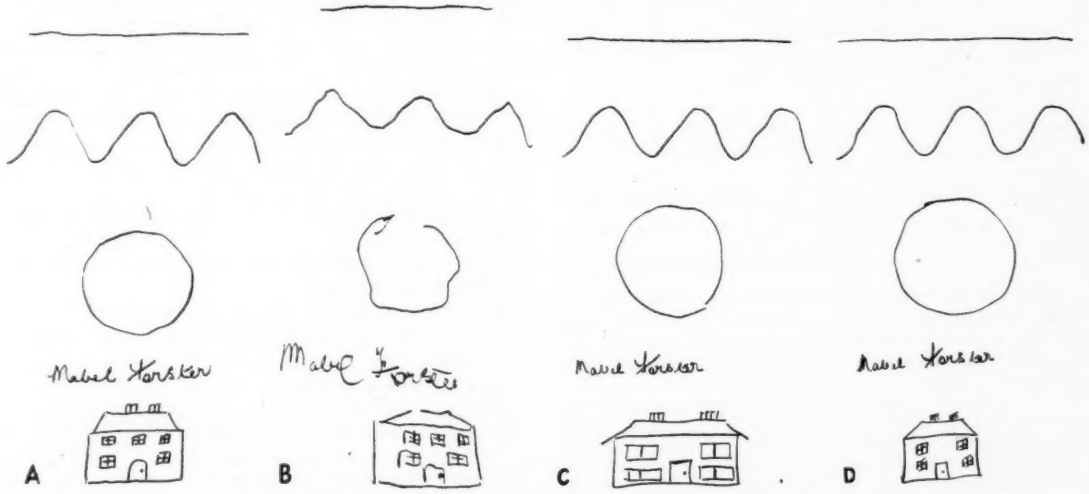
Note: Though inspection of the table makes it clear that there is no statistically significant difference between the two sets of scores, the appropriate test is not obvious. Edwards (1958) suggests a simple method for use in such cases. The table is converted into a 2×2 table in such a way as to minimize the sum of the reciprocals of the class frequencies and a χ^2 test applied. Taking the figures for 30 minutes this rule divides the table between the score of 9 and 10, leading to a value of χ^2 (uncorrected) = 0·63 ($P>0·25$).

The slightly better early results with buthalitone may be expressed in a different way by comparing the times at which the first drawings were made in the two groups of patients. In the thiopentone group the average time was 35 minutes (standard error, 5.6) compared with 29 minutes (standard error, 4.6), and again the difference is one that might easily be due to chance.

Discussion

Buthalitone sodium was first described by Miller *et al.* (1936). In recent years there have been many claims

*See footnote to Table.



Drawings by woman aged 55 (weight 116 lb. (52.6 kg.), buthalitone 1.4 g.): A, when resting before anaesthesia; B, as soon as consciousness was regained; C, at 38 minutes; D, at 63 minutes.

that its properties made it highly suitable for out-patient anaesthesia (Weese and Koss, 1954; Nobes, 1955a, 1955b; Ruddell, 1955; McColl, 1955; Young, 1956; Henderson and Mackett, 1957). On the other hand, its brevity of action (compared with thiopentone) has been disputed by some workers, who have also reported unfavourable side-effects and sequelae (O'Mullane, 1957; Simmons and Blanshard, 1957; Henderson and Mackett, 1958).

An earlier comparison between buthalitone and thiopentone (Simmons and Blanshard, 1957) showed no significant difference between them; the criteria of recovery were the patient's ability to obey verbal commands and to rise unaided to the sitting position. But such a method hardly measures *complete* recovery to normal consciousness. Various ways of doing this have been tried, such as the flicker-fusion frequency of a light source (Nilsson, 1953), and have proved impracticable.

The present method was conceived as a form of intelligence test which might be suitable for use in a busy out-patient department. We have shown that it is in fact practicable and that it combines simplicity with objectivity. It is suitable for almost all patients, making no great demands on their co-operation and inducing no fatigue. Should the experiment be repeated it would probably be wise to specify exact times at which the tests should be made. This would simplify the analysis and obviate the risk of a subjective judgment being used to determine when the first test should be given.

Summary and Conclusion

A new method is described of comparing the rate of recovery from barbiturate anaesthesia. The method is simple and assesses recovery to very near normal consciousness. This method was used in a small trial, and there was found to be no statistically significant difference between buthalitone sodium and thiopentone sodium; it is unlikely, therefore, that there is any great advantage, in respect of rate of recovery, to be gained by using buthalitone rather than the well-established thiopentone.

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"In connexion with forms being prepared by the National Road Safety Council for the reporting of traffic accidents, the Public Health Committee recommended that provision be made on these forms for the recording of information whether the driver at the time of the accident was likely to be under the influence of any therapeutic substance the nature of which should also be specified. This recommendation was made in view of the widespread habit of self-medication and the hazards associated with the use of certain tranquillizing and other drugs freely used by the public." (*Health*, Journal of the Commonwealth Department of Health, Australia, September, 1959.)

LONG-TERM FOLLOW-UP OF 32 PATIENTS IRRADIATED FOR THYMIC ENLARGEMENT IN INFANCY

BY

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Irradiation of the thymus gland in infancy was often practised in the thirties for the treatment of a variety of symptoms thought to be associated with thymic enlargement. Prominent among these symptoms were stridor and attacks of cyanosis, dyspnoea, and syncope. *X*-ray or radium therapy was often employed in such cases, even when radiological evidence for enlargement of the thymus was uncertain. In America, "prophylactic" irradiation was even given to symptom-free infants shortly after birth at one time (Conti and Patton, 1948).

Thymic irradiation went out of fashion in many centres after about 15 years, when it had become apparent that the symptoms ascribed to enlargement of the gland usually cleared as quickly without irradiation. This was fortunate, as it was not realized until some years later that there might be an association between such treatment and the development of thyroid cancer and leukaemia.

Attempts to assess the degree of correlation have been made either by investigating the radiation histories of patients who developed thyroid cancer and leukaemia in childhood (Duffy and Fitzgerald, 1950; Clark, 1955; Stewart *et al.*, 1958; Polhemus and Koch, 1959; and others) or, as in a notable series reported by Simpson *et al.* (1955), by tracing children who had received thymic irradiation in infancy.

In view of the findings an attempt was made to follow up infants who had received irradiation for thymic enlargement at the Middlesex Hospital and at the Hospital for Sick Children, Great Ormond Street. While it is recognized that statistically valid conclusions must be based on larger numbers, this follow-up is presented for its interest and in the hope that it will be possible to combine results from other centres.

It is probable that the subsequent history of such patients sheds little light on the effects of thymic enlargement *per se*, as it is now recognized that true enlargement occurs rarely, and that the thymuses commonly reported as enlarged were probably normal.

A total of 32 infants were found to have received thymic irradiation by deep *x* rays or radium between 1932 and 1950. In all, 27 patients have been traced to the present time and are alive: one has been traced to 1946, and three have died. Only one has remained untraced since treatment was given and has not been notified as having died.

Sex.—Of 31 infants traced, 20 were male. This preponderance of male infants has been observed previously.

Age at which irradiated (Table I).—Of the traced patients, 16 had been treated at the age of 3 months or less. The age at irradiation may well be important, as it will influence the percentage area of body surface irradiated and as there may be an increased sensitivity to radiation at this time.

*Now at the Hammersmith Hospital, London.

Follow-up years after irradiation (Table II).—All but one of the patients had been irradiated more than 10 years ago and 14 more than 20 years. The number of patient-years in the follow-up totals 566. This may be compared with the incidence of leukaemia following irradiation of the thymus as calculated by Polhemus and Koch (1959)—that is, approximately 1/3,300/year. It also appears that a latent period of the order of five to eight years might be expected. The inclusion of follow-up years after the expiry of this period might therefore tend to reduce the apparent incidence of this complication. Similar considerations apply to cancer of the thyroid following thymic irradiation in infancy, but here the latent period ranged from 6 to 24 years in 16 cases reported by Simpson and Hempelmann (1957), and from 5 to 37 years in nine cases reported by Wilson *et al.* (1958).

Dose of Irradiation.—The figures for this were either obtained from contemporary notes or calculated in retrospect from available data. The accuracy of the figures quoted can only be approximate in many cases. The dosage of deep *x* rays directed at the upper mediastinum was stated to be 1,540 r in one case, 1,400 r in one case, 600–900 r in eight cases, and 180–450 r in six cases. The remainder were treated by application for 16 hours of a "radium bib" (Moncrieff, 1938), equivalent to approximately 740 r, assuming a constant distance of 1 cm. from the skin, or by radium applications ranging from 640 mg.-hours as in the "bib" to 1,800 mg.-hours, with other details unspecified.

The rate of irradiation ranged from 800 r in 6½ hours to 180 r in 9 days.

The *presenting symptoms* on referral are set out in Table III.

Subsequent Course.—Three patients were found to have died. One, a mongol, was treated with a "total skin dose 26 r [sic]" at 2–3 months, but died 14 days later with persistent vomiting. The second infant received radium treatment to the upper mediastinum at the age of 7 weeks and was subsequently treated with thyroid tablets until she died suddenly at the age of 5 years. At 18 months it had become evident that she was mentally retarded. She did not appear to benefit from the thyroid therapy, so it is an open question whether her thyroid might have been damaged by the irradiation. The third death occurred at the age of 26 in a motor accident. The post-mortem report mentioned nothing relevant to this investigation.

TABLE I.—*Age at Which Irradiated*

Age in Months:	0–1	2–3	4–6	7–12	13+
Traced	2	12	5	6	3
Died	—	2	—	—	1

TABLE II.—*Follow-up Years After Irradiation*

Years:	0–5	6–10	11–15	16–20	21–25	26–30
Traced	—	1	5*	9	9	4
Died	2	—	—	—	1	—

* One patient was followed up 11 years in 1946.

TABLE III.—*Indications for Treatment*

Laryngeal stridor	21
X-ray evidence*	31
Cough and dyspnoea	11
Syncope, "blue" or "white" attacks (excluding frank grand mal)	9
Other causes†	8

* Cases included under this heading were reported as having abnormal mediastinal shadows, thought to be due to thymic enlargement. Where this was queried in the report the case has nevertheless been included. Most of the films are no longer available.

† Other causes comprised: dilated upper abdominal veins (1), head held askew (2), nose-bleeds (1), breath-holding attacks (1), fits (3).

Associated Abnormal Conditions

Table IV summarizes the associated abnormal conditions found among the 28 surviving patients.

One patient developed a nodular goitre 22 years after irradiation from a radium "bib" at the age of 3 months. (Simpson and Hempelmann (1957) found eight cases of thyroid "adenoma" among 1,400 patients previously irradiated for thymic enlargement, and only one in their control series.) No histological report of this goitre is available. A further patient had a *slight diffuse enlargement of the thyroid* when seen 16 years after irradiation, aged 17. The *neurilemmoma* discovered in another patient was first noticed at the age of 5, situated in the upper part of the right sternomastoid and removed at the age of 14. *Abnormalities of cervical* vertebrae *C 2–6* were found in the patient with the nodular goitre. The vertebral bodies of C 5 and 6 were hypoplastic and fused; there was also some deformity of the articular processes and laminae of C 2 and 3, and an abnormal spur of bone extending downwards from the fourth cervical spine. Radiation exposure can modify vertebral growth (Neuhauser *et al.*, 1952) and may be responsible for the development of exostoses, but the present abnormality was more probably congenital.

TABLE IV.—*Abnormalities and Illnesses Diagnosed, in Relation to Time of Irradiation*

Case	Illness	Onset after Irradiation	Age at Onset
1	Mongol	—	Birth
	Diarrhoea and vomiting	2 weeks	2½ months
	Died	3 ,,	—
2	"Violent catarrh"	"Soon"	*c.* 3 months
	Failure to thrive: continuous treatment with thyroid tablets	,,	?
	Mental defect	16 months	18 months
	Died suddenly	5½ years	5½ years
3	Nodular thyroid goitre.	13 ,,	13 ,,
	Abnormality of cervical vertebrae		(congenital)
4	Slight diffuse thyroid enlargement	16 ,,	17 ,,
5	? Growth retardation (but final stature normal)	5 ,,	5 ,,
6	Neurilemmoma in sternomastoid	5 ,,	5 ,,
7	Pulmonary tuberculosis	21 ,,	22 ,,
8	Bronchiectasis; lobectomy	15 ,,	15 ,,
9	"Chesty"	?	?
10	,,	11 years	11 years
11	,,	?	?
12	,,	?	"Till age of 14"
13	Asthma	13 years	13 years
14	Pneumonia	3 ,,	3 ,,
15	Diarrhoea and vomiting for 3 weeks*	3 days	3 months
16	Diarrhoea	1 month	9 ,,
17	Cerebral palsy; mental defect	—	"From birth"
18	"Highly strung"	5 years	5 years
19	Grand mal	11 ,,	13 ,,
20	? ,, ,,	—	2 months

* It is possible that the diarrhoea and vomiting were a direct sequel to the radiation given.

The number of *respiratory illnesses* may be related to the high incidence of respiratory symptoms presenting at the time of irradiation in infancy. No effect on *growth* could be detected, though one male of 5 ft. 6 in. (168 cm.) at the age of 23 years was suspected of growth retardation at the age of 5. There were no cases of *leukaemia*, but the chance of encountering one in such a limited series is small. It may be that most of the patients reviewed here have passed the danger period for the consequential development of thyroid cancer or leukaemia, but larger numbers of cases will have to be

collected before any definite statement can be made concerning the risk throughout the subsequent life of these patients.

Summary

Thirty-two patients who received irradiation for suspected thymic enlargement in infancy between 1932 and 1950 are reviewed. Thirty-one of these have been traced. Three have died, one possibly from the acute effects of the radiation. One case developed a nodular goitre 22 years after the irradiation, another had slight diffuse enlargement of the thyroid at the age of 17, and another had a neurilemmoma removed from the neck at the age of 14. There were no cases of leukaemia.

I thank Professor Alan Moncrieff, on whose suggestion this work was undertaken; Dr. E. W. Hart for allowing me access to the records of patients he followed up in 1946; DR. M. Lawrence, latterly of the Hospital for Sick Children, Great Ormond Street, and the Cancer Registration Section of the Registrar-General's Office, Somerset House, for assistance in tracing the patients. An abstract of this paper was read at the Royal Society of Medicine in May, 1959.

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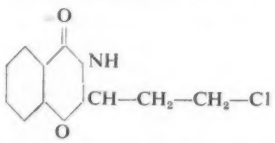
Preliminary Communications

Chlorthenoxazin — A New Analgesic

During 1957 136 suicides were attributed to overdose of aspirin and 41 further accidental deaths resulted from its use. An increasing number of authors refer to the hazards resulting from persistent haemorrhage into the gastro-intestinal tract which is frequently associated with aspirin therapy. In the face of this disadvantage one must assume that the continued use of aspirin as the standard mild analgesic is due to the lack of an acceptable alternative.

Biochemical research during the past decade has been extensively concerned with compounds of the benzmethoxane series, and in 1951 the substance 2-(β-chlorethyl l)-2,3-dihydro-4-oxo-(benzo-l-3 oxazin) was submitted to pharmacological investigation.



To establish its analgesic action, pilot testing of mice by the tail-tip method of Haffner (1929) was followed by extensive experiments using the hot-plate method of Chen and Beckman (1951). By the latter method Kadatz (1957) showed that a dose of 152.4 mg./kg. was capable of eliminating the pain reaction in 50% of a group of 30 mice. This compares with a comparable dose of acetylsalicylic acid of nearly 300 mg./kg. It was also shown to possess antipyretic and anti-inflammatory activity.

The LD_{50} for rats was shown to be 0.73 g./kg. by intraperitoneal injection and 10 g./kg. by mouth. Toxic doses produce central depression with respiratory failure. High individual doses of 3 g. by mouth were given to dogs without ill effect (weight of animals 9–14 kg.). The long-term toxicity studies on dogs showed no harmful effects after six months on a dose of 0.2 g./kg. daily by mouth. The treated animals remained normal as regards growth and behaviour, and their blood picture, coagulation time, and prothrombin time were normal at the end of the test period.

In the rat a dose of 100 mg./kg. was completely absorbed after 15 hours and none appeared in the faeces. In man 75% of an oral dose appears as metabolites in the urine within 33 hours and complete excretion takes at least 40 hours. By comparison, 4 g. of salicylic acid is completely excreted in the urine within 15 hours.

The metabolites of chlorthenoxazin (*B.P.*) have been studied by means of paper chromatography and can be estimated quantitatively after acid hydrolysis in the form of total salicylates and total gentisate. Estimations of serum levels in human subjects showed a maximum seven hours after administration. This compares with a maximum serum level of acetylsalicylic acid three hours after ingestion, suggesting that chlorthenoxazin is absorbed and excreted more slowly than aspirin and that it tends to accumulate within the body after repeated dosage, giving a higher serum level after some days' administration.

The problem of the assessment of the analgesic activity in man was approached initially by means of small-scale double-blind trials in patients suffering constant pain from osteoarthritis (D. W. and P. H. K.). Compound codeine tablets and aspirin were used as controls, and the results showed that the effect of the two substances, measured by the subjective response of the patients, did not differ significantly. It was confirmed that chlorthenoxazin has a period of action up to 50% longer than aspirin or compound codeine tablets; there were no noticeable side-effects. One of us (P. H. K.) used chlorthenoxazin in an experimental study on pain induced in volunteers by injecting 6% saline into the interspinous ligament. Statistical analysis of the results revealed an analgesic action equivalent to paracetamol.

A further controlled trial was carried out with "valtorin" (compound tablet containing 250 mg. of chlorthenoxazin and 200 mg. of phenacetin) on 1,000 patients following dental extraction (P. M. P.). The analgesic effect of the compound was equivalent to that obtained with compound codeine tablets.

Preliminary experience in these trials suggests that chlorthenoxazin is relatively free from gastro-intestinal irritant action. Seven subjects, six of whom were known aspirin "bleeders," showed no evidence of occult blood in the stools after administration of 1,800 mg. daily (the average therapeutic daily dose).

Experience with the long-term use of the drug, which extends in a few cases to as long as 18 months, has revealed no diminution in haemoglobin levels.

Work with the drug is continuing, and, if our present results are confirmed, chlorthenoxazin should prove a most useful addition to the present range of mild analgesics.

We are grateful to Messrs. C. H. Boehringer Sohn, Ingelheim am Rhein, for supplies of chlorthenoxazin and valtorin.

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Practical Experience with the Peak Flow Meter

Many elaborate instruments are available for measuring expiratory flow rates, but few are suitable for use in the consulting-room, in the factory, or at the patient's own bedside. The peak flow meter whose workings were described by Wright and McKerrow (1959) has been used by us both in clinical practice and in epidemiological surveys, and has proved itself to be a practical aid in the investigation of chest conditions.

RESULTS IN NORMAL PERSONS

The mean reading for 105 males was 53.7 (equivalent to 537 litres per minute) and for 74 females the reading was 38.0. These normal values were based upon 69 staff at Queen's College, Dundee, 30 staff at Ashludie Chest Hospital, and 80 symptom-free flax-workers.

In men the blowing power was found to decline 0.29 unit (S.E. 0.10) for each year's increase in age, and for every extra inch of height the blow increased by 1.44 units (S.E. 0.23). Weight had no significant effect, and the values for women did not change significantly with age, height, or weight.

The peak flow readings were compared with expiratory flow rates (3/4 second forced expiratory volumes) measured either on a spirometer of the type described by Bernstein, D'Silva, and Mendel (1952) or on the modified Gaensler (1951) apparatus. In order to mitigate the effect of age, sex, and body-build, it was found convenient to use the ratio of 40 times this volume—that is, the E.F.R. 40 of Kennedy (1953)—to the predicted value of the maximum breathing capacity (M.B.C.) of Needham, Rogan, and McDonald (1954).

COMPARISONS WITH OTHER INSTRUMENTS

During a survey in a flax factory and flax mill, measurements were obtained on both the peak flow meter and the Mendel spirometer for 65 subjects. For 41 men the coefficient of correlation between the two instruments was 0.81, and for 23 women 0.62. These can be compared with the coefficient of 0.86 obtained by Higgins (1957). The mean values of various categories for the two instruments are shown in the Table.

Mean Values for the Two Instruments

	No.	Peak Flow Meter (As % of 60 for Men or 40 for Women)		Spirometer $\frac{\text{E.F.R.40}}{\text{Pred. M.B.C.}} \times 100$	
		Best of 3 (%)	Average (%)	Best of 3 (%)	Average (%)
Symptom-free ..	13	95	91	96	89
Byssinosis (alone) ..	9	89	84	91	99
Simple bronchitis ..	19	79	75	83	81
Complicated ,, ..	5	73	69	78	74
Emphysema	4	36	35	36	34
Miscellaneous conditions*	15	74	71	82	79

* These include bronchospasm (9), upper respiratory catarrh (4), bronchiectasis (1), and hypertension (1).

The coefficient of variation (standard deviation/mean as a percentage) was approximately 30% for both instruments, whether the best or the average reading was used. This represents the variation between subjects. The variation between tests on the peak flow meter at different times in the same subject was 10%, and the variation between blows at the same test in the same subject was only 6%; this last was only one-half of the corresponding variation for the spirometer (11.5%).

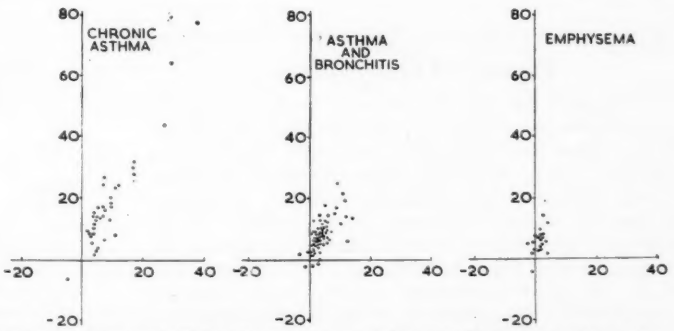
RESPONSE TO BRONCHODILATOR DRUGS

Forty-five hospital patients with bronchospasm were tested with each of four drugs (subcutaneous adrenaline, intravenous aminophylline, and prednisolone and isoprenalline by insufflation) as a guide to maintenance therapy. Their improvement, shown on the Graphs, was estimated by measurements before and after the administration of the drugs, using both the peak flow meter (horizontal axis) and a Mendel or Gaensler spirometer (vertical axis). The patients have been divided into three categories in order to demonstrate the differences in response that may occur.

Those diagnosed as chronic asthma show the best correlation between the two measurements. Those in the asthmatic bronchitis group show less spectacular improvement and the scatter is wider. The correlation is least in the emphysema group, who show little response to the drugs used.

DISCUSSION

The only occasion when the peak flow meter failed to reproduce the results obtained with other spirometers



Response to bronchodilator drugs as measured by peak flow meter and by spirometer. Vertical axis represents change in spirometer readings after administration of drugs. Horizontal axis represents change in peak flow readings.

was in a study designed to show the effect of byssinosis in flax-workers during the course of the working day, as had been previously demonstrated by Schilling (1956) in cotton-workers. Otherwise the instrument has been found to give results comparable to those obtained using more sophisticated apparatus. It is fully portable, and can be used without lengthy preparations. It is speedy in operation, the time needed to take three readings and explain the use of the instrument being only three minutes, as contrasted with five minutes for the Gaensler apparatus, its nearest rival.

The peak flow meter measures a component of respiration slightly different from that measured by the spirometers. It measures the initial peak, lasting about one-hundredth of a second, compared with the three-quarter second measured on the spirometer, and it is more sensitive to the muscular element in respiration. It does, however, separate respiratory conditions with an efficiency equal to that of other instruments in common use.

SUMMARY

Wright's flow meter has been compared with other spirometers in normal persons on the staff of Queen's College, Dundee, and Ashludie Chest Hospital, in flax-workers, and in hospital patients undergoing treatment with bronchodilator drugs.

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Medical Memoranda

Long-acting Glyceryl Trinitrate in Angina Pectoris of Out-patients

"Nitroglyn," the preparation used, contains specially coated granules of glyceryl trinitrate which are released slowly from the gastrointestinal tract. Each tablet contains 1/10 gr. (6.5 mg.) of glyceryl trinitrate, which causes peripheral vasodilatation, measured in fingers, lasting for about five hours (Mann, 1956). It has therefore been proposed as a form of treatment for angina pectoris, but so far there have been no controlled trials of the preparation during daily activity. Consequently, we decided to try the effect of nitroglyn on out-patients suffering from typical angina of effort.

Methods.—The trial was conducted on 10 patients suffering from angina pectoris of effort lasting not more than one minute; all showed electrocardiographic changes and were regular users of glyceryl trinitrate. Nitroglyn tablets and an indistinguishable dummy tablet were used. The tablets were taken first thing in the morning and after lunch for two periods of a fortnight each. The fortnightly sequence was randomly determined and was not known to any of us. The patients were also given unlimited numbers of ordinary glyceryl trinitrate tablets (1/130 gr.; 0.5 mg.) to chew only when required and not as a prevention for expected attacks. They were asked merely to record the number used. They were not warned of side-effects, and during the trial none were noticed.

Results.—Only seven patients completed the course satisfactorily. Two abandoned it after the first fortnight, during which they had received the active tablet thinking it of no value, and the third patient could not tell us how many ordinary tablets she had taken. As the Table shows, there is no striking difference in the amount of ordinary glyceryl trinitrate used by the patients during a fortnight, whether they were on nitroglyn or on the dummy tablet.

Average Number of Tablets Per Patient Taken During a Fortnight

	Nitroglyn (1/10 gr.; 6·5 mg.) Twice Daily	Dummy Tablet Twice Daily
No. of glyceryl trinitrate tablets (1/130 gr.; 0·5 mg.) taken during a fortnight	43	43·6

The nitroglyn tablets used were fully active in that they produced, in volunteers, typical headache lasting three and a half to four hours. This long action, however, was not an effective prophylaxis in our patients suffering from typical short attacks of angina of effort.

The trial was not designed to test nitroglyn in patients with severe angina occurring at rest, or lasting for longer than a minute; its value in such patients must therefore remain an open question.

We are grateful to Professor A. C. Dornhorst for help in the preparation of this communication. The nitroglyn and the dummy tablets were generously supplied by the Key Corporation, Pharmaceuticals, Miami 37, Florida, U.S.A.

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REFERENCE

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"There is great scope for the missionary doctor who is ready to accept responsibility, willing to forgo material advancement, and to lead a life of service. Pioneer work in primitive conditions; the widest possible clinical experience; an almost unlimited sphere of preventive medicine; teaching and research—all these are included in the scope of medical work through the Church overseas. There is opportunity for specialists in many fields, as well as for the doctor who is willing to tackle the enormous rural problems of health and disease." (*Careers in the World Church, No. 3.*) Inquiries should be sent to the secretary of the Medical Missions Department, S.P.G. House, 15, Tufton Street, London, S.W.1.

Reviews

A GAP REPAIRED

Leukemia. By William Dameshek, M.D., and Frederick Gunz, M.D., Ph.D. (Pp. 420+xi; illustrated. $15.75.) New York, London: Grune and Stratton. 1958.

It is now twenty years since Claude Forkner produced his famous monograph on *Leukaemia and Allied Disorders.* It remains a mine of useful information but unfortunately has never been revised. Dameshek and Gunz have therefore done a real service to haematology in writing a new book on leukaemia and thus repairing the gap in the literature.

The early chapters deal with the history, classification, prevalence, aetiology, and cytology of leukaemia. The problem for the writer on leukaemia is whether to treat it as one disease or as several, and the authors get over this difficulty by giving us one chapter on leukaemia as a whole, one on the different varieties, and one on certain special manifestations such as anaemia and haemorrhage. A similar combination of holism and separateness is used in the approach to treatment. Intermediate chapters deal with diagnosis, prognosis, and the myeloproliferative disorders. There are 141 excellent black-and-white illustrations and four colour plates. For so well documented a book the index is on the thin side.

This is an admirable monograph which haematologists and all students of medicine will welcome, and Dr. Dameshek's enthusiasm is so contagious that we can take his high-lighting of "low percentage" leukaemia, di Guglielmo's syndrome, and the myeloproliferative disorders in our stride. Treatment is well done, particularly the importance of knowing when to stop.

> "It appears that the tendency in recent years, notably amongst the junior men in the hospital, is to keep on treating the patient to the very last gasp of life. Thus, it is the rare patient who dies *sans* oxygen tent, all manner of intravenous tubes and infusions, and last-moment 'stimulants.' Transfusions are often given until almost the last hours of life, even after it has been repeatedly demonstrated that all they do is to improve the patient's status temporarily. Is it possible that in some cases we are carrying our therapeutic efforts too far, that we are prolonging life beyond any possible useful period and that in so doing we are bringing needless suffering to the patient and his family?"

If there is a fault in the monograph—and it is a minor one—it is a certain lack of bite. This is in part due to want of the conciseness which made Forkner's monograph so notable; much has been read and marked but it has not always been sufficiently digested. Perhaps, too, it is because, as Dameshek and Gunz point out, we still have not penetrated to the heart of the problem of leukaemia although we know so much more about it than Forkner did.

L. J. WITTS.

EPONYMS IN OBSTETRICS AND GYNAECOLOGY

Obstetric and Gynaecologic Milestones. Essays in Eponymy. By Harold Speert, M.D. (Pp. 700+ix; illustrated. £5 5s.) New York, London: Macmillan Company. 1958.

If the title and subtitle of this delightful book were reversed (as they are on its fly-leaf) a more accurate impression would be gained of its contents. These consist of 79 separate essays, each based on an anatomical landmark, instrument, syndrome, operation, or manipulation to which is attached the name of one or more men. By this means some of the famous personalities in the history of obstetrics and gynaecology are introduced and their lives and work outlined. The eponyms themselves are described so far as is possible in the original words of the men whose names they carry, and this, together with reproductions of photographs, title-pages, and the like, gives a strong flavour of authenticity. It also illustrates how time and misquotation can twist and distort. Credé, for example, would never recognize what now passes as his manœuvre.

Dr. Speert generally makes clear the circumstances and background of the inventions and discoveries, and this often shows that priority credited to a particular individual is ill deserved. The majority of the stories are quite fascinating, especially those that apply to the remote past. Many of the more modern eponyms, however, lack the aura of history; some are national rather than international, and, from the European standpoint, not always well chosen.

The author is certainly more at ease with the past than with the present, and, having for reasons of space to select only a certain number from a host of eponyms, might well have given us more of the names which are traditional throughout at least the whole of the English-speaking world. This criticism is more favourable than adverse, indicating as it does that the reader's appetite is whetted to such an extent as to demand further helpings of the first course before being faced with a rather less satisfying second. Having learned about those whose names are immortalized in the form of Fallopian tube, Sims's position, Cloquet's node, Hegar's sign, Bandl's ring, Pfannenstiel's incision, and the like, we are left wondering about Aveling's repositor, Auvard's speculum, Braun's hook, and many more. Perhaps this is being greedy. As it is, the book should find a place on every gynaecologist's desk, there to be picked up and enjoyed piecemeal during every spare 10 minutes.

T. N. A. JEFFCOATE.

BREAST CANCER

Breast Cancer. The Second Biennial Louisiana Cancer Conference, New Orleans, January 22–23, 1958. Edited by Albert Segaloff, M.D. (Pp. 257; illustrated. 37s. 6d.) St. Louis, Missouri: C. V. Mosby Company. London: Henry Kimpton. 1958.

This volume contains the papers read at the Second Biennial Louisiana Cancer Conference held at New Orleans in January, 1958, together with the discussions which took place. The conference was divided into sections on "Basic Biology," "Definitive Treatment," and "Hormone Therapy," and at the conclusion of each the contributors answered questions from the audience.

In the paper on "Epidemiology of Cancer of the Breast," Emerson Day, from the Sloane Kettering Institute, reviews the incidence of breast cancer in recent years. He brings out the well-recognized phenomenon of double peaks in the age incidence of this disease, and relates this to a hormonal mechanism operating maximally at two different age periods. The fact that in all large series the disease is very slightly more common in the left breast is held to argue that a traumatic factor is likely to play a part in the incidence of breast cancer. Other factors such as marital state,

the effect of benign breast disease, and of heredity are fully discussed.

In the paper on "Biologic Variability," by Ian Macdonald, a comparison is made between survival rates in Wade's well-known series of 802 cases of untreated breast cancer, and the rates in treated cases; this is greatly to the advantage of the latter. Nevertheless, the author points out that the biological nature of the growth is perhaps more important in determining survival than is the treatment. He distinguishes two main biological groups, one with a very rapid growth rate in which, with whatever treatment, the prognosis is desperate; and another with a slower progression in which treatment is an important factor in survival. Macdonald distinguishes these two groups in an original and unusual way by their sensitivity to a test dose of irradiation. If the growth responds well it is regarded as belonging to the rapidly growing group for which surgery is contraindicated; if there is a poor response, it is regarded as a slow-growing neoplasm for which surgery should be prescribed with a good prognosis.

Sternberg discusses the multi-focal origin of many breast cancers, and describes "carcinoma *in situ*." The cytology of breast secretion is regarded as an unreliable diagnostic tool. Grading of breast tumours is thought to be somewhat unrewarding, as the nature of the growth varies so considerably from place to place. This section —the most interesting in the book—closes with a consideration of the present position of hormones and viruses in the genesis of murine breast cancer.

In the section on definitive treatment the most revealing part occurs in the discussion—obviously carried on with that huge enjoyment and absence of rancour which the natural *bonhomie* of the clinician, allied to his almost total ignorance in this field, leads us to expect. Here is the usual floundering about and complete inability to produce any conclusion based on more substantial evidence than a man's opinion. It is sad to think that these rhetorical exercises will be curtailed when the idea of the controlled clinical trial finally exerts its influence on the minds of these eager and thoroughly well-disposed persons.

The third section epitomizes recent knowledge on hormone therapy.

The book is important for the earlier chapters which give the general surgeon a good idea of the trends of modern thought in epidemiology and provide the expert with references to all the important papers. The book, as might be expected, is beautifully produced and well illustrated.

HEDLEY ATKINS.

THE DISABLED ARM

Functional Bracing of the Upper Extremities. By Miles H. Anderson, Ed.D. Edited by Raymond E. Sollars. (Pp. 463 +xv; illustrated. 72s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1958.

This book is the work of an essentially practical man, and springs from the research he did with a team at the University of California on artificial limbs and other appliances. It is, in effect, a large picture-book with short and useful descriptions. Most of the illustrations are from photographs and line drawings. There are details of hand splints, arm braces, and many devices to improve the function of a disabled upper limb. The manufacture and uses of the appliances are clearly described, so that the reader knows the tools and materials required. The principles are well illustrated, particularly in hand-splinting devices which prevent deformity and improve function. The pictorially described hand "gadgets" differ little from those known in this country. Useful instructions are given for making holders for a pencil, cigarette, and electric-razor, feeders, and other devices. Stabilizers and assisting apparatus are described for functional disability at elbow and shoulder. The author gives a few words of advice on gadget tolerance which are, indeed, words of wisdom, and of greater importance to the patient than the concepts of biomechanics and information on rubber bands and ball-bearings. Dr. Anderson was particularly interested in providing instruction and training courses, and he claims that this book is the first of its kind. It is difficult to detect an appreciation of the published work done in other countries—particularly in Britain and Canada—before the advisory committee instituted by the Veterans Administration was formed in 1946.

The provision of apparatus to increase the function of a limb with weak muscles has become a problem for solution by the combined work of doctors, engineers, and others. Hence this book will be of great value to surgeons and ancillary workers in the field of rehabilitation.

ST. J. D. BUXTON.

SURGICAL ANATOMY

Callander's Surgical Anatomy. By Barry J. Anson, M.A., Ph.D.(Med.Sc.), and Walter G. Maddock, M.S., M.D., F.A.C.S. Fourth edition. (Pp. 1,157+xvii; illustrated. £7 7s.) Philadelphia and London: W. B. Saunders Company. 1958.

In writing a book on surgical anatomy one of the difficulties must be to know how much anatomy and how much surgery should be inserted. For students the emphasis should be on anatomy; for surgeons, on surgery. If an attempt be made to cater for both students and surgeons there is the danger that the book becomes too large. *Callander's Surgical Anatomy* has proved its worth by its popularity for more than a quarter of a century, but we think it is more suitable for the surgeon than for the student. It contains more than 1,100 pages and over 1,000 illustrations, and is much too heavy to hold in the hand while reading. The anatomy is in some places too detailed—for example, the variations of the sigmoid and its mesocolon need not be so elaborate, and other percentage variations could with advantage be curtailed. Despite this minor criticism the book is an excellent production, and Drs. Anson and Maddock have well maintained the high standard attained by previous editions.

ZACHARY COPE.

HEAD AND NECK SURGERY

Surgery of the Head and Neck. By Robert A. Wise, M.D., and Harvey W. Baker, M.D. (Pp. 319; illustrated. 73s.) Chicago: Year Book Publishers, Inc. London: Interscience Publishers Limited. 1958.

This volume is one of a series of handbooks of operative surgery of which a number have already appeared. It manages to compress much information into 300 pages equally divided between text and illustrations. It is intended as a manual of practical surgery, and the didactic advice it contains concerns surgical procedures rather than the reasons for them. Surgical operations in the head-and-neck region have greatly increased in scope during the past ten years, but, now that major

operations are increasingly performed by specialists, the average general surgeon in this country may have little experience of them. However, he will find much of what he needs to know in this book, which serves admirably as a revision course of partly forgotten procedures. The principles involved can also often be adapted in other fields. The authors' extensive experience in the surgery of this region is revealed in many neat modifications of standard methods. Unfortunately, they give very few references—phrases such as " several excellent texts on plastic surgery " are not very helpful.

In dealing with fractures of the facial bones the authors have omitted all discussion of mid-line fractures, which produce the so-called dish-face deformity. Perhaps they feel that this very difficult fracture should be handled in special centres, but this is not always possible, and the extra space required to give some guidance on the subject would have been well worth while. It is also surprising that the extended excision of the superior maxilla to include the orbit is omitted. The management of the closure in these cases is of great importance, and an extra page or two spent here would have been welcome. Nevertheless, on the whole the authors can be congratulated on the choice they have made both of insertion and omission. In the treatment of tumours the emphasis throughout is on surgical methods; as in much American literature, the values of irradiation are understressed and the dangers of post-irradiation malignancy somewhat overstated.

Many of the drawings are excellent, but some are in a complicated line technique which lacks the clarity of half-tone or scraper-board methods. The text is to the point, and the print is excellent. This little manual should rank high in its particular series.

MAXWELL ELLIS.

ASPECTS OF CARDIOLOGY

Terceiro Curso de Cardiologia. Arritmias. By Eduardo Coelho, with the collaboration of A. Bordalo e Sá, António Sousa Borges, Mário Gomes Marques, Eduardo de Paiva, Artur de Oliveira, Salomão Sequerra Amram, Fernando de Pádua, and José Filipe da Costa. (Pp. 319+vi; illustrated. No price.) Lisbon: Imprensa Médica. 1958.

Quarto Curso de Cardiologia. Electro-Vectocardiografia. By Eduardo Coelho, with the collaboration of Manuel Joaquim Sousa Ventura, A. Sales Luis, Salomão Sequerra Amram, A. Bordalo e Sá, A. Lopes Pimenta, and Fernando de Pádua. (Pp. 380; illustrated. No price.) Lisbon: Imprensa Médica. 1958.

There are numerous contributors to the third and fourth courses in cardiology edited by Dr. Coelho, of Lisbon. The third course discusses the disorders of rhythm. Extrasystoles are classified by their site of origin. Auricular escape is noted as a rare phenomenon. A form of auriculo-ventricular block caused by extrasystoles is described as something new. Auricular fibrillation is thought to be due to vagal hyperexcitability and myocardial hypoxia; this may be associated with intracellular deficiency in potassium. The fourth course is concerned with the theory of electrocardiograms and also vectorcardiograms. There are sections on the U wave; on intraventricular conduction; and on the curves of hypertrophy and infarction. Each section is summarized in English, as well as in French and German, but the summaries do not give much indication of what the section's contents really are. Many of the illustrations leave much to be desired, particularly the vectorcardiograms. There is no index, but quite a full list of references.

TERENCE EAST.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

Napoleon Immortal. The Medical History and Private Life of Napoleon Bonaparte. By James Kemble, Ch.M., F.R.C.S. (Pp. 307+xi; illustrated. 28s.) London: John Murray. 1959.

Arteriopatie Obliteranti degli Arti Inferiori. By G. Marcozzi, S. Messinetti, and G. A. Ricci. (Pp. 195; illustrated. L. 5,800.) Rome: Edizioni Mediche e Scientifiche. 1959.

L'Ostruzione Intestinale: Fisiopatologie e Clinica. By Professor Edmondo Malan with 14 collaborators. (Pp. 311; illustrated. L. 4,800.) Rome: Edizioni Mediche e Scientifiche. 1959.

Fermente—Hormone—Vitamine: und die Beziehungen Dieser Wirkstoffe Zueinander. Volume I. ***Fermente.*** Edited by R. Ammon and K. Myrbäck. Third edition. (Pp. 564+xx; illustrated. DM. 96.) Stuttgart: Georg Thieme Verlag. 1959.

La Flebografia Vertebrale Transomatica. Originale Metodica d'Indagine Angiografica dei Plessi Rachidei e Azigos-cavali. By G. Marcozzi, S. Messinetti, L. Saracca, and M. Colombati. (Pp. 159; illustrated. L. 6,500.) Rome: Edizioni Mediche e Scientifiche. 1959.

More Medical and Other Verses. By Alex. E. Roche. (Pp. 35+viii. 5s.) London: H. K. Lewis and Co. Ltd. 1959.

Tools of Biological Research. Edited by Hedley J. B. Atkins, D.M., M.Ch.Oxf., F.R.C.S.Eng., Hon.F.A.C.S. Introduction by Sir Cyril Hinshelwood, P.R.S. (Pp. 183+xvi; illustrated. 37s. 6d.) Oxford: Blackwell Scientific Publications. 1959.

Clinical Prosthetics for Physicians and Therapists. A Handbook of Clinical Practices Related to Artificial Limbs. By Miles H. Anderson, Ed.D., Charles O. Bechtol, M.D., and Raymond E. Sollars. (Pp. 393+viii; illustrated. 84s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Cutaneous Manifestations of the Malignant Lymphomas. By Samuel M. Bluefarb, B.S., M.D., F.A.C.P. (Pp. 534+xiii; illustrated. £6 4s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Die Papierelektrophorese. Methoden und Ergebnisse. By Ch. Wunderly. Second edition. (Pp. 202; illustrated. DM. 18.80.) Aarau and Frankfurt: H. R. Sauerländer and Co. 1959.

Narcotics: Lingo and Lore. By J. E. Schmidt, Ph.B.S., M.D., Litt.D. (Pp. 199+xiv. 32s. 6d.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Readings in Psychoanalytic Psychology. Edited by Morton Levitt, Ph.D. With 24 contributing authors. (Pp. 413+xiv. 70s.) London: Staples Press. 1959.

The Householder's Electrical Guide. A Practical Guide to Repair, Maintenance and Installation of Electrical Appliances, Accessories and Materials. By F. C. Searle. (Pp. 127; illustrated. 10s. 6d.) London: Stanley Paul. 1959.

Forensic Medicine. Observation and Interpretation. By A. Keith Mant, M.D.(Lond.). (Pp. 262+vii; illustrated. 42s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

A Practice of Anaesthesia. By W. D. Wylie, M.A., M.B. (Cantab.), M.R.C.P., F.F.A.R.C.S., and H. C. Churchill-Davidson, M.A., M.D.(Cantab.), F.F.A.R.C.S. (Pp. 1,056+xv; illustrated. £5 5s.) London: Lloyd-Luke (Medical Books) Ltd. 1960.

Peripheral Facial Palsy: Pathology and Surgery. By Karsten Kettel, M.D. (Pp. 341; illustrated. £6.) Oxford: Blackwell Scientific Publications. 1959.

Jewish Medical Ethics. A Comparative and Historical Study of the Jewish Religious Attitude to Medicine and its Practice. By Rabbi Dr. Immanuel Jakobovits. (Pp. 381+xlii. 42s.) New York: Philosophical Library. London: H. Pordes. 1959.

Police Work with Juveniles. By John P. Kenney and Dan G. Pursuit. Second edition. (Pp. 383+xx. 76s.) Springfield, Illinois: Charles C. Thomas. Oxford: Blackwell Scientific Publications. 1959.

Klinische Chirurgie für die Praxis. Edited by Professor Dr. O. Diebold, Professor Dr. H. Junghanns, and Professor Dr. L. Zukschwerdt. In 4 volumes. Volume I, Part 1. (Pp. 184+iv; illustrated. DM. 36.) Stuttgart: Georg Thieme Verlag. 1959.

BRITISH MEDICAL JOURNAL
LONDON
SATURDAY JANUARY 2 1960

O TEMPORA !

That *The Times* should devote two leading articles attacking the B.M.A. for not accepting an advertisement for its popular health magazine is difficult to understand, especially as the attack is based upon surmise and not facts. As we recently pointed out,[1] *The Times*, in company with some other newspapers, refused during the war to publish an advertisement of the Central Council for Health Education designed to help control intestinal infections—which were then a cause of great concern to the health authorities. So *The Times* starts from a shaky position in its thunderous admonition to the B.M.A. to "clear itself of the charge that now hangs over it of having given in to a minority." Before firing such a broadside, *The Times* should have first made sure of the facts. It should, above all, have been accurate. It has not been.

What is the evidence? *The Times* evidently took its lead from a report in the *Sunday Express* of December 6. A reporter on the staff of this paper had learnt that on the agenda of the Council, meeting four days later, was a request from the Family Doctor Committee for the opinion of the Council on the advisability of publishing in *Family Doctor* and "Getting Married" an advertisement of that highly reputable body the Family Planning Association. The agenda was marked "Confidential" and "For the use of members of Council exclusively." The *Sunday Express* reporter obtained the views of a Roman Catholic surgeon in Harley Street on this, and also the views of the F.P.A. itself—which, incidentally, got a handsome and free advertisement through the large circulation of a popular Sunday newspaper. The Roman Catholic surgeon told the *Sunday Express* that when "Getting Married" was published (in 1959) "a large number of Roman Catholic doctors were ready to resign from the B.M.A. . . ." He added: "I cannot say whether we would take the same action over this advertisement, because I have not seen what form it is in, but certainly there is great feeling over this issue." There was no threat in this moderate statement. A similar and even more moderate statement—from the Guild of St. Luke, SS. Cosmas and Damian—was before the Council and was the only communication received from Catholic doctors in spite of the publicity on Sunday four days before the Council met.

In its issue of December 10, the day after the Council meeting, *The Times* reported the fact that the F.P.A. advertisement was not to be published in *Family Doctor* publications "before further consideration by the Association's Council." *The Times* report ended with the following highly misleading statement: "Last year's edition of 'Getting Married' was withdrawn after certain Roman Catholic doctors protested." It thus blazed a trail of error and misrepresentation. Wide public offence was caused by an article in "Getting Married" 1959 entitled "Is Chastity Outmoded?" Protests came from numerous religious denominations—from individual churchmen, from the *Baptist Times*, from the Church of England Moral Welfare Council, from the *Church of England Newspaper*, from the *Church Times*, from prominent spokesmen of the Church in Scotland ("Church reaction was strongest in Scotland," according to the *Daily Mail*)—and from Roman Catholic spokesmen and doctors. Lay criticism was summed up in the following comment on the controversial booklet in *The Yorkshire Post*: "It is not in the least difficult to realize what harm it will do."

We much regret having to stir the embers of a fire which, but for *The Times*, was quietly dying down. But it is necessary to adduce at least some of the evidence to show how grossly misleading was its report of December 10, with its curious and exclusive reference to Roman Catholics as the cause of the withdrawal of "Getting Married" 1959. The B.M.A. may or may not have been wise to withdraw the booklet. The point to be established is that it withdrew it because of the great offence caused by part of the booklet to all sections of religious opinion, and to lay opinion as expressed in some responsible newspapers.

Unfortunately the uninformed have followed *The Times's* misleading lead. Its first and regrettable inaccuracy was followed by its leading articles of December 12 and December 21, which accused the B.M.A. of succumbing to the pressure of a Roman Catholic minority—and the second of these made the completely unwarranted statement that the B.M.A. had admitted it. *The Times* is its only witness for these misstatements—misstatements which correspondents to the *B.M.J.* have adopted. It makes a charge on the basis of one report in a Sunday

[1] *Brit. med. J.*, December 19, 1959, p. 1392.
[2] See *Supplement, Brit. med. J.*, December 19, 1959, p. 196.

newspaper, and on the imaginative flights of its own writers, and then tells the B.M.A. to clear itself.

We can state unequivocally that the B.M.A. Council did not succumb to the pressure of a Roman Catholic minority But there are obviously grave doubts about the wisdom of publishing in a popular health magazine issued by the B.M.A. to the public —and read, among others, by teen-agers and by the immature—an advertisement which might be held to give the green light to contraceptive practices. For the benefit of *The Times* and those others who have jumped to hasty and unwarranted conclusions, we should state that the Council did not vote against the publication of the advertisement. How it would have voted is anybody's guess. The chairman of the Family Doctor Committee intervened at the point when a vote was about to be taken by asking permission to withdraw the advertisement from consideration for the time being; and Council voted in favour of giving this permission.[2]

It is highly regrettable that *The Times* and others have discovered in this second controversy over "Getting Married" another Gunpowder Plot. It is unfortunate that the floodlight has been turned on the Roman Catholics. As a minority in a Protestant country they deserve the tolerance traditionally shown in this country to minorities. They have every right to express their convictions. They have no right to attempt to dictate, nor indeed in this instance have they done so. The B.M.A. would not give in to threats of resignation, holding that this is a poor kind of response from members who disagree with it on an item of policy. The various divisions of the Protestant Church—and in England the Lambeth Conference—have recognized the right and the need of married persons to adopt contraceptive methods for the planned spacing of births in a family. Correspondents to this *Journal* are right in drawing attention to these facts. The general body of opinion in Britain, as expressed by the Established Church, by responsible laymen, and probably by the great majority of doctors, approve of the approach to the problem by such responsible bodies as the Marriage Guidance Council and the Family Planning Association. But no one—whatever his private beliefs or public protestations—can be otherwise than deeply perturbed by the prevailing sexual *mores*, by the exploitation of sex by the cynical, by the effect of the pressures and examples of those who should know better upon impressionable young people who have never had it so good. They have forgotten that Freud said something to the effect that civilization is inhibition. All this is but part of the background to the decision the Family Doctor Committee and the Council have, in concert, tried to arrive at in deciding whether to publish in a popular health magazine issued by the B.M.A. to the public an advertisement which might be held to point in a certain direction.

After all we have a National Health Service which makes available to the whole population medical skill and advice. Any young married couple can go to their general practitioner, whom they can choose freely, for advice on the problems of marriage and the techniques of contraception. And the general practitioners have valuable allies in such organizations as the Marriage Guidance Council, the Family Planning Association, and, if they wish it, the various religious groups of this, that, or the other denomination. The position of the general practitioner as the family adviser, counsellor, and friend is paramount in this situation, and is something which in the present hullabaloo has been lost sight of. O Tempora ! O Mores !

ANTIBIOTICS AND HOSPITAL INFECTION

The opinion has been expressed, perhaps not in all seriousness, that we should be better off if penicillin and other antibiotics had never been discovered. This is to ignore benefits they have brought of which we are not reminded in everyday hospital practice in northern latitudes. But, in bringing to light what is happening in such practice, the report by Dr. Maxwell Finland and his colleagues[1] at the Boston City Hospital provides very serious food for thought, if not for alarm. This report, based on the case records of that hospital, analyses the frequency of bacteriaemia, meningitis, and empyema (classified as due to pneumococci, various streptococci or staphylococci, and various Gram-negative organisms) and the mortality of these infections for the years 1935 (pre-sulphonamide), 1941, and 1947, so as to show the full effect of sulphonamides and penicillin respectively, and for the years 1951, 1953, 1955, and 1957 to show the effects of the later antibiotics. This analysis discloses a remarkable change of which everyone must be aware, although its extent and the magnitude of its effects have not been revealed before. Among the cocci, pneumococci and haemolytic streptococci, which cannot acquire resistance to penicillin, have become progressively less common causes of serious infection. On the other hand,

[1] Finland, M., *et al.*, *J. Amer. med. Ass.*, 1959, **170**, 2188.
[2] Knorr, K., and Wallner, A., *Disch. med. Wschr.*, 1957, **82**, 1473.

bacteriaemia and meningitis due to staphylococci, the most adaptable to antibiotics of all organisms, have multiplied many times in frequency. Among Gram-negative organisms of the "coliform" group, every species named has become a more frequent cause of both bacteriaemia and meningitis, including some which were very uncommon causes of such conditions twenty years ago, notably *Ps. pyocyanea, Proteus,* and *Klebsiella aerogenes.* The mortality from meningitis and empyema diminished somewhat, but that from bacteriaemia, after falling during the early part of this period, has risen since to a level about 50% higher than in 1935. That generalized bacterial infections should be causing more deaths now, with the great range of antibiotics currently available, than there were even before the introduction of the sulphonamides is indeed a warning that we have not advanced in this field of therapeutics as some may suppose. We may even be losing ground.

Possibly not all hospitals could furnish such startling figures as these. Allowances must be also made for other changes: people are living longer, and much of the mortality disclosed here is among older patients. Surgery has become more adventurous, and the greater susceptibility to infection resulting not only from surgical but even from some forms of medical treatment may deserve a share of responsibility. But undoubtedly most of the blame must be laid at the door of a few species of bacteria. Some that were most feared in the past have almost faded into insignificance, but as a result of the widespread use of antibiotics hospitals have become populated by new bacteria of two kinds. One is the staphylococcus. This was always a common cause of serious infection, but what is now new about it is its frequent resistance to penicillin and to other antibiotics besides. The other is a group of hardy coliform bacilli which in the past rarely did more than local damage in the urinary tract and elsewhere; these are naturally resistant to most of the major antibiotics, and sometimes susceptible only to those with drawbacks of toxicity and difficulty of administration. This is indeed a formidable change in the nature of infection, and concerted measures are needed to meet it.

An important contribution to the problem of antibiotic-resistant staphylococcal infection is the study which has now been in progress for nearly two years at the Postgraduate School of Medicine at Hammersmith Hospital. The results of this are reported by Dr. Mary Barber and her colleagues at page 11. Efforts to control this kind of infection began with a series of hygienic measures which must have had some part in the results achieved. A policy for the use of antibiotics was then introduced, to be observed throughout the hospital. The detailed instructions are reproduced in the report: their main features are general restriction of use, particularly for prophylaxis, abandonment of the use of penicillin except in specified wards, and the invariable prescription of two antibiotics together, or one antibiotic with a sulphonamide, instead of a single drug. There are good reasons for believing that when two agents are acting together bacterial resistance is less likely to develop, and the main object here was to reduce the antibiotic-resistant population. Such an experiment has in fact been made on a small scale before. K. Knorr and A. Wallner[2] confined the use of antibiotics in a maternity unit so far as possible to tetracycline and oleandomycin, with the result that the frequency of staphylococcal resistance to some antibiotics fell by about 50%, although that of resistance to penicillin fell only from 87 to 73%. In the much larger and more protracted study at Hammersmith a similar effect was observed. Among strains isolated from patients, the frequency of penicillin resistance fell from 74 to 52% and of resistance to both penicillin and tetracycline from 51 to 36%. Strains possessing multiple resistance were responsible for most of the more serious infections which occurred. Dr. Barber and her colleagues discuss the question whether these strains are intrinsically more virulent, but it is difficult to distinguish such an intrinsic property from the consequences of simple resistance to therapy. However this may be, the incidence and mortality of these infections fell during this period. There was also a diminution in the frequency of penicillin resistance in carrier strains from nurses. The results might have been even better but for the repeated importation of resistant strains in patients transferred from other hospitals.

Some of these changes for the better seem to have begun before the antibiotic policy was adopted and may therefore be credited in part to other measures, but in their continuation this policy may reasonably have been concluded to have played a major part. Does this evidence amount to a sanction for a general policy of combined treatment? If so, a serious increase in cost must be faced if the principle is also accepted that in combined treatment each antibiotic must be given in its full individual dose. During this study the consumption of penicillin fell, but that of other antibiotics—and these are much the more expensive—was approximately doubled. In any further trial of such a policy the restrictions imposed here on the use of penicillin might well be removed.

CHRONIC DISABLEMENT FROM NEUROLOGICAL DISORDERS

Patients with severe and permanent disabilities, including young adults, are mostly to be found in geriatric wards, or waiting with misgivings in other hospitals for transfer to such wards. Some are in voluntary societies' homes; many more are at home imposing heavy burdens on their families until physical deterioration, especially incontinence, or a social upheaval finally causes their admission to hospital; and others with lesser disabilities are in the care of local authorities. A recent investigation carried out in and near London by an almoner, Miss A. Whitaker, with the help of a grant from the Nuffield Foundation has thrown more light on the needs of these unfortunate people. The 314 "chronic sick" patients she studied were aged 15 to 55, and with medical advice from Dr. M. E. Fearnley she classified them according to the disorder from which they suffered. Five out of six were found to have neurological disease, one-third of the total having multiple sclerosis.

The end-result in many patients such as these is severe paralysis, and sometimes mental deterioration. Young patients in geriatric hospitals or confined in welfare homes with elderly people are often found to be bored and disillusioned, lacking congenial company and sufficient occupation, and cut off from the outside world. A few, with loss of mental powers or as a result of long familiarity with their environment, come to accept it. To those with independent and vigorous minds such unsuitable accommodation can be acutely distressing.

Clearly the younger patients with these serious chronic diseases should be separated from the very old or degenerated and cared for in more appropriate surroundings than a geriatric ward. Separate "young" wards in long-stay hospitals are one solution: completely independent units, with as little as possible of the usual institutional regimen, are probably better. But there are many difficulties in the way. There are only small numbers of these younger patients in any one district, and it must be possible for their relations to visit them easily and for other links with society to be maintained. The nursing units must be small, so that the patients can be grouped according to temperament and abilities, and, more important, so that those who are relatively well need not be in close contact with others on the downward grade. Full facilities for treatment, including physiotherapy and occupational therapy, must be available in the building, which should have good day-rooms and every device for encouraging independence. The patients should be able to feel that even terminally they need not be moved elsewhere for care. Yet some of them will survive to old age and pose a further problem. Thus the administration of such places will have to be particularly flexible and imaginative.

Intermittent hospital care with periods at home is often much better for the patient than endless confinement to hospital. Most families would co-operate thankfully in such arrangements. The sense of a burden shared, with the certainty that there will be periods of real relief, is a great encouragement to the particular member of the family who nurses the patient and often enables her to continue much longer than she would otherwise have done. The care of the patient at home can also be made much less of a burden by the provision of nursing help, aids to movement such as wheelchairs, and by structural adaptations in the home. There is evidence that the statutory powers under which help of this kind can be given are not being used to the full. Further, local authorities might provide day or part-day attendance. The principle of the day-hospital could possibly be widened to meet the needs of the chronic invalid, young or old. Above all, forward planning for the individual patient is essential. All too often at present the interest of general hospitals and neurological departments wanes after the possibilities of diagnosis and initial treatment are exhausted. Patients and their families are introduced too late, if at all, to the domiciliary aids and hospital services which are available for the chronically disabled.

Who is best placed to plan the care of these patients? The geriatric physician already deals with most identical problems in older patients: he is concerned with long-term nursing, with disabilities and rehabilitation, with domiciliary care; he has daily contact with local-authority services and must necessarily adopt a medico-social approach in helping to overcome his patients' difficulties. If he is willing to care for the younger chronically disabled patient also—and it must be said that not all geriatric physicians regard this as their proper function—there is hardly anyone in a better position to help the general practitioner to plan ahead and provide the necessary continuity of care. In most hospital regions geriatric physicians are acting in this way, but before their help can be fully effective two requirements must be met—properly designed accommodation for the chronically disabled younger patient, and close liaison between neurologist and geriatric physician in the earlier stages of the patient's illness.

SHAPE OF THE TRACHEA

The trachea is a well-behaved structure, and, as it is not often the site or source of serious disease, demands little attention from the clinician, except when he is concerned with the mechanics of respiration. As both ends of the trachea may move, observation of its behaviour is complicated. On inspiration the larynx may descend, ascend, or remain unchanged—its maximum movement in either direction being 6 mm.[1]

In their studies of tracheal movement W. S. Holden and G. M. Ardran[2] used bronchography and cine-radiography, these providing an ideal method of following the bronchial tree throughout respiration. In 50 bronchograms, taken from subjects between 12 and 65 years of age and free of bronchial abnormality, they found that during deep inspiration the trachea increases

its diameter by about one-tenth and its length by about one-fifth—the latter increase being equivalent to about 2.5 cm. The main bronchi resembled the trachea, but in more distal ones the range of movement was greater. In coughing, the trachea and bronchi showed the narrowing and shortening typical of a forced expiration, both during momentary closure of the larynx and after it had opened—that is to say, there was no dilatation of trachea and bronchi, the upward movement of radio-opaque material being seen only in large bronchi. In violent paroxysms the reduction in diameter of the trachea was as much as one-half to two-thirds. In health, then, the trachea is extremely mobile, able to extend and shorten with great rapidity.

Recently R. S. Harris[3] has investigated this extensibility, using necropsy material including tracheas from 20 newborn infants and 31 adults. By applying weights to the carina he determined the point at which "further loading produced much less extension." In tracheas from infants and middle-aged and senile people this point of "full extension" was reached with a load of 20, 80, and 140 g. respectively. The increase is given as a percentage of the initial length; over successive decades the extensibility decreased by about 3%—in the full-term infant the mean was 46% (range 32.5–64.5%), while in adults over 70 the elongation was about 20% and the range was narrow. It would be interesting to know whether these tracheas were from healthy or diseased lungs, what the length and diameter were before weights were applied, and how precise was the point of full extension. Harris relates the extensibility of the trachea in the baby to the importance of supero-inferior expansion of the lung, since at this age diaphragmatic breathing is so important, the ribs being relatively horizontal and the diaphragmatic surface about 35% of the total pleural surface, in contrast to 15% in the adult of 35.[4]

Yet in spite of its great mobility in health the trachea can, without giving rise to symptoms, be grossly distorted and contorted. One of the most dramatic clinical illustrations is in tracheopathia osteoplastica, when the trachea may be a rigid bony tube discovered only post mortem, as shown in a recent report by D. A. L. Bowen.[5] But, if there is little evidence at present that disability arises from disturbed tracheal function, it must yet be recognized that little attention has been directed to its functioning in disease. The changes Harris has described need to be related to dynamic studies such as those of Holden and Ardran to show what are the changes with age, in length and diameter, in both healthy and diseased lungs, and what is the behaviour, in quiet and deep respiration and with coughing, of the dilated and tortuous tracheas often found in cases of pulmonary disease. The wider use of cine-radiography, with image amplifiers of larger fields, may be expected to establish the significance of these questions.

[1] Mitchinson, A. G., and Yoffey, J. M., *J. Anat. (Lond.)*, 1947, **81**, 118.
[2] Holden, W. S., and Ardran, G. M., *J. Fac. Radiol. (Lond.)*, 1957, **8**, 267.
[3] Harris, R. S., *Thorax*, 1959, **14**, 201.
[4] Dally, J. F. H., *J. Anat. (Lond.)*, 1908, **43**, 93.
[5] Bowen, D. A. L., *J. clin. Path.*, 1959, **12**, 435.

OESTROGEN EXCRETION IN GYNAECOLOGICAL DISORDERS

"The conservative therapy of functional gynaecological disorders does not at present rest on particularly strong foundations. . . . It might be expected that a more complete knowledge of the hormonal production and excretion of the pituitary and ovarian glands would lead to a more rational approach in the treatment of these disorders." Thus do J. B. Brown, R. Kellar, and G. D. Matthew[1] preface their report of a prodigious amount of work in which they have correlated excretion of urinary oestrogen with clinical and pathological findings in 75 patients. This is a very important paper, for there has been nothing like it before in either scope or detail. Moreover, we are promised further papers from the Edinburgh group on gonadotrophin and progestogenic function in these disorders.

In general the authors detected two main trends of oestrogen excretion. In the first they found more or less constant levels of urinary oestrogens in post-menopausal patients, cases of amenorrhoea with inactive endometrium, patients with anovulatory cycles, and some patients with cystic glandular hyperplasia. In the second, the level of urinary oestrogen fluctuated periodically; this was found in patients with ovulatory cycles and in some cases of cystic glandular hyperplasia.

The patients could be grouped further on the basis of the endometrial histology, which was found to correlate closely with the level of urinary oestrogens. Atrophic endometria, found in many post-menopausal cases, were associated with the excretion of less than 10 μg. of oestrogen in 24 hours. Patients with early proliferative endometria had occasional phases of bleeding and excreted between 7 and 18 μg. of oestrogen in 24 hours. Patients with fairly regular anovulatory cycles and proliferative endometria excreted 15 to 30 μg. in 24 hours. Patients with a constant output of oestrogen, whose endometria showed cystic glandular hyperplasia, excreted betwen 25 and 40 μg. in 24 hours.

In the group of patients whose oestrogen levels fluctuated there were first of all those with normal cycles. In these, the pattern of oestrogen excretion is characterized by the occurrence of two peaks, the first and most pronounced (35–100 μg. in 24 hours) coinciding with ovulation and the second, more prolonged (17–87 μg. in 24 hours), with function of the corpus luteum. Menstrual bleeding begins approximately 14 days after the ovulation peak and takes place from a secretory endometrium. The other patients showing fluctuations in excretion of oestrogen were some of the cases of cystic glandular hyperplasia. In these, however, the raised levels of oestrogen were maintained for longer and were usually greater than those found in the normal menstrual cycle. Bleeding episodes were associated with rising, falling, or persistently raised levels of urinary oestrogen.

The findings, thus briefly summarized, do scant justice to the enormous amount of detailed work carefully

[1] Brown, J. B., Kellar, R., and Matthew, G. D., *J. Obstet. Gynaec. Brit. Emp.*, 1959, **66**, 177.

recorded and discussed in the paper by Brown and his colleagues. This is undoubtedly a notable step towards our better understanding of the pathogenesis of many common menstrual disorders. Nevertheless, as the authors point out, "It is clear that, although a great deal of useful information can be derived from urinary oestrogen assay alone, it is essential to relate those results to the levels of other hormones, particularly progesterone and the gonadotrophins, in order to assess and treat cases of dysfunctional bleeding in the gynaecological patient." It might also be added that, though such studies must advance the knowledge on which clinical practice is based, for the ordinary day-to-day handling of most of these patients the information obtained from relatively simple procedures—endometrial biopsies, vaginal smears, and basal temperatures—is entirely adequate. In other words gynaecologists cannot expect their departments of clinical pathology to carry out routinely the elaborate hormone investigations performed by the Clinical Endocrinology Research Unit of the Medical Research Council.

POLIOMYELITIS AND WEATHER

The epidemiology of acute poliomyelitis has been a source of special interest and speculation in Great Britain since the disease changed from a sporadic to an epidemic nature in 1947. Associations between the incidence and social and other conditions found in one epidemic area have not been repeated in other outbreaks. The summer maximum of poliomyelitis, which is an unusual feature of an epidemic disease, and the almost constant time of the year when the incidence starts to increase, certainly suggests a relationship with the weather. The second large outbreak—in 1949—occurred during a hot dry summer and favoured the theory of a dustborne infection, but the following larger outbreak in 1950 occurred in a cold wet summer. In the hot dry summer of 1959 poliomyelitis has been at a very low ebb, with the number of notifications at their lowest since the disease first appeared in epidemic form, but inoculation probably accounts for a part of the fall. If atmospheric conditions favour the survival and spread of the virus it seems that the meteorological factors favouring a rise in incidence are more complex than can be classified in descriptive terms. It is, of course, possible that the connexion between poliomyelitis and the weather is an indirect one, and that other conditions which are influenced by the weather cause poliomyelitis to appear in a clinical form.

Meteorological factors which might influence the rise and spread of poliomyelitis have been the subject of a number of studies, of varying thoroughness, in Great Britain and America. W. H. Bradley and A. E. Richmond[1] examined the effect of dry-bulb temperature and vapour pressure on the incidence of poliomyelitis in England and Wales during the six years 1947–52. They found that the seasonal rise each year did not begin until a minimum temperature and humidity had been reached, but the rise in incidence did not necessarily begin when these figures had been attained. Variations in temperature and humidity did not influence the incidence of poliomyelitis or initiate the seasonal fall. The latest attempt to establish a relationship between meteorological factors and the incidence of poliomyelitis is by C. C. Spicer.[2] He considered variations in the dry-bulb temperature, relative humidity, and vapour pressure during 1947–56. The analysis was very detailed, entailing the use of electronic computors, and the incidence of poliomyelitis was related to meteorological readings with various time lags. The temperature and relative humidity, but not the vapour pressure, showed some association with the incidence of poliomyelitis, though these relationships varied from year to year. While there is a prima facie case that the incidence of poliomyelitis depends on the weather, it is unlikely that the meteorological readings so far used have any value in predicting the size of an outbreak.

[1] Bradley, W. H., and Richmond, A. E., *Monthly Bull. Minist. Hlth Lab. Serv.*, 1953, **12**, 2.
[2] Spicer, C. C., *Brit. J. prev. soc. Med.*, 1959, **13**, 139.

AUTOANTIBODIES IN ULCERATIVE COLITIS

During recent years great interest has been aroused by the discovery of auto-immune reactions in some types of thyroid disease, such as Hashimoto's disease and myxoedema, and also in certain other diseases, such as diffuse lupus erythematosus, Addison's disease, and acute nephritis. From such observations has sprung up the general concept of auto-immune disease, which Sir Macfarlane Burnet has recently reviewed in the Croonian Lectures for 1959.[1] It is therefore natural to look for the existence of auto-immune reactions in any disease of which the aetiology still eludes us. One such disease is ulcerative colitis, for which many theories of causation have been advanced without satisfactory proof that any of them is a sufficient explanation.

O. Broberger and P. Perlmann[2] have now reported the existence of circulating antibodies against normal colonic extract in the sera of children suffering from ulcerative colitis. In order to obtain antigen from human colon unmixed with bacteria, they prepared their antigenic extract from the colons of children who had died during their first day of life without having fed, carrying out the extraction by means of phenol-water. Out of 30 children with ulcerative colitis, 22 showed positive precipitation reactions when their sera were tested against colonic extract, whereas there were no positive reactors among 10 normal children and 32 others with a variety of diseases. These and other experimental results obtained by Broberger and Perlmann strongly suggest that auto-immune processes are involved in ulcerative colitis. However, it still remains to assess the significance of this finding, an issue which is evident to the authors themselves, because they remark: "The question then arises: are the demonstrated antibodies responsible for the destructive processes, or are they only immunological by-products of no pathogenetic significance?" In any event, we can be sure that these observations will be a spur to future work aimed at a better understanding of a baffling disease.

[1] Burnet, M., *Brit. med. J.*, 1959, **2**, 645 and 720.
[2] Broberger, O., and Perlmann, P., *J. exp. Med.*, 1959, **110**, 657.

Drug Treatment of Disease

PROGESTOGENS AND THEIR CLINICAL USES: PART I

BY

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PROGESTOGENS

Until recently, progesterone itself and ethisterone (ethynyltestosterone, anhydrohydroxy progesterone, pregneninolone) were the only available progestational agents. Now a whole range of new steroids possessing some, though not necessarily all, of the properties of progesterone, have been produced by the steroid chemists. Some of these substances are considerably more potent than progesterone itself, while others appear to possess special properties of their own. In consequence, a great deal of interest in progestational agents has been reawakened and much research has been carried out, though regrettably little of it in Great Britain. This paper will discuss the more important progestogens from the standpoint of therapeutics.

Progesterone

The intramuscular route is most commonly used for the administration of progesterone, in oily solution, because it is only feebly active by mouth. It has also been administered as vaginal pessaries, but this, too, is an uneconomical method.

Since the average daily output of progesterone during the luteal phase of the menstrual cycle is about 20 mg., it is unlikely that a lower daily dose can have much therapeutic effect. In pregnancy, the daily output is probably 100 to 400 mg., so then daily doses must be of at least 100 or 200 mg. to have much value. These doses are substantially higher than those commonly used in the past, and they are not always well tolerated. Indeed, there have been reports (e.g., Wilkins *et al.*, 1958) of the birth of female pseudohermaphrodites of non-adrenal origin to mothers receiving intensive progesterone therapy during pregnancy, though of course this is a rarity. Progesterone has also been administered in the form of micro-crystals, to produce a depot effect, and as implants.

Progesterone Microcrystals.—Administered by intramuscular injection, they are considered to exert an effect lasting three or four weeks. Some patients experience quite severe pain at the site of injection—which obviously limits their usefulness.

Progesterone Implants.—Progesterone in the form of cylindrical fused pellets has been implanted, mainly in cases of habitual abortion. The pellets must be placed deeply, in muscle, beneath the deep fascia by means of a trocar and cannula, as otherwise they are very likely to extrude. Pellets of 25 and 50 mg. are mostly used; 100-mg. pellets are seldom retained.

17α-Hydroxyprogesterone Capronate.—Because of the fleeting effects of intramuscular injections of oily solutions of progesterone, usually necessitating frequent, repeated injections, 17-α-hydroxyprogesterone capronate ("primolut-depot") was introduced as a long-acting ester (Junkmann, 1954). This is available in strengths of 65, 125, and 250 mg. per ml. of oily solution, is well tolerated, and exerts an effect lasting for about seven days. Two intramuscular injections, each of 125 mg., seven days apart can produce a full secretory endometrial response in oestrogen-primed castrate women.

Ethisterone.—Though this has been widely used as an orally-active progestogen for many years, there is no doubt that it is of very low potency, at any rate as judged by the amount required to produce a full secretory endometrial response in oestrogen-primed castrate women. Thus, whereas a daily intramuscular injection of 20 mg. of progesterone for 14 days can produce a late secretory endometrium, the daily oral dose of ethisterone required to produce an equivalent response was found to be 250–300 mg. (Wied and Davis, 1958)—i.e., 12–15 times as much. It is doubtful if progesterone orally (or sublingually) is any less potent than ethisterone by the same route (Bickers, 1949).

The daily doses of ethisterone usually administered (5–100 mg.) can seldom produce anything approaching a full therapeutic effect.

Newer Progestational Steroids

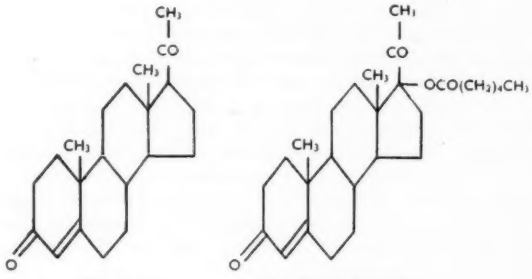
A large number of synthetic steroids, some derivatives of progesterone, others nortestosterone derivatives, have, in recent years, been tested for progestational activity. Much information on these is collected in the report of a Symposium on New Steroid Compounds with Progestational Activity held in 1957 in New York (Rakoff, 1958). From the clinical point of view, interest centres mainly on some of the nortestosterone derivatives, which alone will be considered further here.

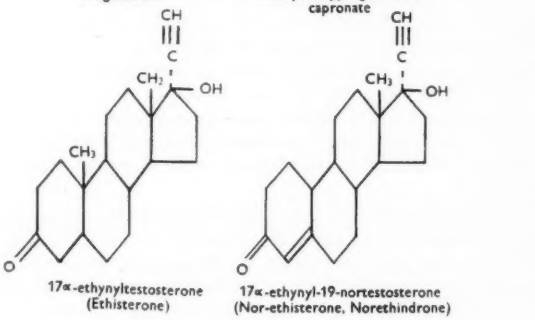
Several of the nortestosterone derivatives have considerable progestational activity. In some—for example, 19-nortestosterone, 17α-methyl-19-nortestosterone (methyloestrenolone), and 17α-ethyl-19-nortestosterone (norethandrolone)—nitrogen anabolic activity is prominent, and indeed overshadows progestational potency. Androgenic properties are also possessed by these steroids; their potencies are probably very similar, and indeed differ little, if any, from that of methyltestosterone itself (Saunders and Drill, 1956; Overbeck and de Visser, 1956). On the other hand, 17α-ethynyl-19-nortestosterone (norethisterone, norethindrone ("primolut N")) and norethynodrel ("enavid"), in addition to their progestational activities, also have oestrogenic but not androgenic action; for clinical use as progestogens, therefore, these substances would appear to be preferable. All these nor-steroids appear to be powerful pituitary inhibitors.

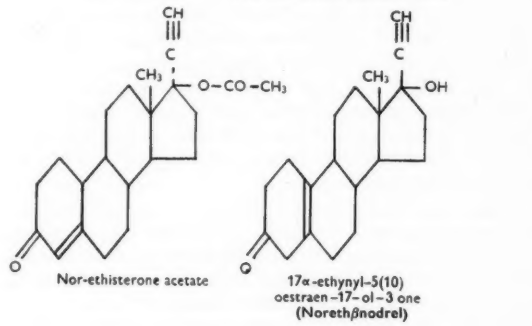
Norethisterone Acetate.—This is the latest and most potent oral progestogen developed by Junkmann. Potts (1958) found that a total dose of 10–40 mg. given over ten days to oestrogen-primed castrate women produced a full secretory endometrial response. In women with secondary amenorrhoea, Swyer (1959) found a rather higher dosage necessary (40–80 mg.). Both authors

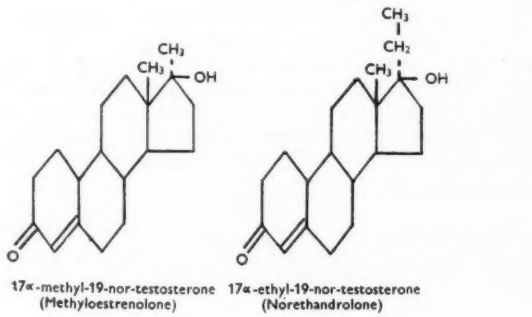
agree that norethisterone acetate is about three times more potent than norethisterone and that it is well tolerated—even in high doses, up to 18 mg. a day.

Norethynodrel.—This steroid differs chemically from norethisterone only in the presence in the first ring of a double bond in the 5–10 position instead of the 4–5 position. In addition to its marked progestational activity (about equivalent to that of norethisterone), it has inherent weak oestrogenic properties. These are further enhanced by the presence of ethinyloestradiol-3-methyl ether, which occurred in the original preparations as a contaminant. It was found that, when pure norethynodrel was administered, break-through bleeding was more common than with the contaminated preparation, and therefore in enavid the proportion of ethinyloestradiol-3-methyl ether is deliberately increased so that each tablet contains 0.15 mg. with 9.85 mg. of norethynodrel.









Very extensive investigations have been carried out with enavid, mainly in the United States, and its properties are well known (see Rakoff, 1958; Conference on Enavid, 1958).

Briefly, when administered to normal women in a dose of 10–20 mg. daily, from the fifth day of the cycle, it causes a rapid secretory transformation of the endometrium—within about 5 days—but instead of the glands passing into a typical late secretory appearance they soon undergo what has been termed "exhaustion atrophy." At the same time the stroma is stimulated and a predecidual appearance is commonly found in biopsies taken on the nineteenth or twentieth day of the cycle. More prolonged treatment produces endometrial appearances similar to those found in mid- and late pregnancy. By means of continuous treatment, at a sufficiently high dose, menstruation can be postponed, apparently indefinitely. On cessation of treatment the usual withdrawal bleeding occurs. In some patients break-through bleeding occurs before treatment is stopped, but doubling the dose usually leads to prompt arrest of bleeding. If two or three successive cycles of treatment have been given, it is usual for ovulation to be somewhat delayed in the next cycle, so that the first spontaneous period may be a week or 10 days late.

Some patients show intolerance to enavid; the proportion so affected has varied with different observers, but on the whole it is probably not less than 20%. Nausea, vomiting, general malaise, dizziness, breast discomfort, and headaches are the symptoms most commonly experienced. In some patients they are mild and soon wear off, especially if the treatment is taken at night; but in others they are sufficiently severe to make continued treatment impossible.

Like the other nor-steroids, enavid appears to have potent pituitary-inhibiting effects. As a consequence, it prevents ovulation, by virtue of which it has proved to be a highly effective oral contraceptive (Pincus *et al.*, 1958). In animal experiments it has not shown pregnancy-maintaining properties (Saunders and Drill, 1958).

(*Part II, with list of references, will appear next week.*)

A report has recently been issued describing the results of a pilot survey undertaken on 120 people over the age of 65 living mainly in and around London. The work was undertaken as a preliminary aid to planning wider surveys of old age; and, along with other projected studies, it has arisen from several years' discussion between social scientists in many countries. "By an organized attempt," say the authors, "to investigate the problem of the aged in different Western countries, using identical methods, we hope to rouse interest in a problem common to many nations. We also hope to arouse interest in the variations to be found in different countries. Finally, we hope to prepare the way for more frequent international collaboration, both in carrying out social research and in providing practical help with social problems." (*The Personal, Family, and Social Circumstances of Old People,* International Association of Gerontology, Social Science Research Committee, European Section, by Peter Townsend and Brian Rees, Department of Social Science, London University.)

THE IDENTIFICATION OF TABLETS

BY

J. D. W. WHITNEY, M.B., M.R.C.S.

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It is an everyday occurrence for doctors to be faced with the question of identification of unknown tablets—in fact, large sums of money and much time are often expended in analysing tablets in cases of poisoning. Often when doctors are seeing patients of their colleagues, whose records are consequently not available, there is difficulty because they are not certain of the exact nature of the tablets which the patient is receiving. On occasion, also, a busy general practitioner may not be able to record fully the tablets prescribed, and in this situation he is in difficulty when wishing to represcribe them. Patients sometimes bring in tablets to the doctor which they allege they have used for themselves on previous occasions and in which they have very great faith. They want to know if they can use them again, and it is obviously a great help to the doctor if he is sure of their composition. If, as often happens, the patient has a large quantity of tablets in stock, it is difficult to differentiate between the various types of tablets, particularly as the packets issued by chemists (to patients) are not usually labelled.

Sometimes patients are discharged from hospital with a large number of enigmatic boxes containing similar tablets; the doctor wishing to make an alteration in dosage of one of the drugs prescribed has difficulty in differentiating between the tablets, as, for example, tab. digoxin 0.25 mg. *B.P.*, tab. phenobarbitone ½ gr. *B.P.*, and tab. ephedrin. ½ gr. *B.P.* Consequently, in making a day-to-day alteration in treatment, the doctor, in order to be absolutely sure, may have to prescribe a completely new set of tablets with the amended dose—in which case it is obviously sensible for the boxes to be labelled.

If there was an infallible way of identifying tablets so that the doctor would know their nature but the patient would not, the above difficulties would be eliminated, and in some cases reduction in the prescription bill could be easily effected. It is for these reasons that I have felt prompted to make certain suggestions regarding the identification of tablets.

A method of identification by colour is not practicable for three reasons. Firstly, with the addition of colouring matter to tablets there is often a variation between batches, and if identification were to be done on a colour basis there would be no allowance for such variation. Secondly, with the number of tablets currently available there are not enough colours to go round. Thirdly, there is often a variation between the actual colour of the tablet and a printed colour plate. Hence it is clear that, to be infallible, means of identification must be based on die-stamping.

A large number of pharmaceutical firms mark their own tablets with the firm's name—for example, CIBA—or the initials of their firm in the form of a motif, I.C.I., M.S.D., S.K.F., etc., or a code name common to that firm's tablets—for example, "diskets" or "tabloid." As many tablets are white and of the same size, it is often very difficult to tell them apart. For example, tablets of both "lergine" and "lanoxin" (B.W. & Co.) have the identical "tabloid" mark, and even when placed side by side the difference between the two cannot easily be distinguished.

A System of Numbering Tablets

I do not view with disfavour the marking of any firm's products by the methods stated above, but I do suggest that there should be a means of easy identification by a system of numbers, which could be common to that firm's products and stamped on the tablets, together with the firm's trade mark or initials—for example, tab. lanoxin could have a die-marked figure in the centre of the tablet, and lergine could have a different number, thereby facilitating the identification of such tablets from one another. I.C.I. have a system of empirical marking, which is an individual approach to the problem, but there are difficulties with this in that the marking cannot be easily described; for example, when phoning the chemist it is easier to say "I.C.I.8" than "I.C.I. on one side and on the other side a vertical dot and dash on one-half of the tablet and reversed on the other half," even supposing that the chemist has the identification chart for I.C.I. tablets available.

Some firms—for example, M. & B.—have been bold enough to mark the name of the product on the tablet. This is of course ideal so far as the doctor is concerned, but it tells the patient the name of the drug which he is receiving, whereas by the method envisaged the patient could merely know the name, initials, or trade mark of the firm, and only chemists and doctors would be able to identify the product from the firm's own numbers.

Another valid criticism against putting the name of the product on the tablet is that, if the product has a long name and the tablet is small, the consequent abbreviation could well be misleading. However, in the suggested system, if the tablet is small the initials of the firm (up to three letters) could be placed on one side and the number (up to three digits) on the other side; this would facilitate identification.

I am told that it will soon be possible effectively to mark sugar-coated tablets, and I believe it is also possible to mark other coated tablets. It is to be hoped that these tablets will in time be included within the scope of this scheme.

Capsules.—These can easily be marked with a system of different-coloured bands, somewhat akin to that employed in the electronic industry for the identification of resistors. I suggest that each firm manufacturing capsules could have a fixed coloured band for its exclusive use, while a combination of width, number, and colour of other bands could identify the different products, and, of course, strengths, for that firm. In support of this suggestion, here again it would not be easy for the patient to find out what was in the capsules, unless he had access to the proposed scheme of identification cards. Alternatively, it might be possible to print code letters and numbers on the same lines as for tablets.

B.P. Products

The question of *British Pharmacopoeia*, *British Pharmaceutical Codex*, and *British National Formulary* tablets must be considered. I feel that this scheme

should also include *B.P.* products, but that in view of the number of these involved it would probably be necessary to run several parallel series such as: B.P.A. 1–999, B.P.B. 1–999, B.P.D. 1–999, and so on up to B.P.Z.

With the majority of tablets it should be possible to get most of the letters and numbers on each side. Using the series indicated above, approximately 25,000 combinations would be available. This should easily cover the *B.P.* and allow plenty of additions to the *B.P.* list, and, of course, with the inevitable deletions there would be potential space for use in later years. There could be incorporated in the *B.P.* series a special *B.P.C.* series to cover the *Codex* tablets, or, alternatively, the *Codex* tablets could be included in the overall *B.P.* series. The latter suggestion would seem more practicable, as it might save a change of die with the compilation of a later *B.P.*

An alternative scheme for *B.P.* tablets would be to allocate code initials to all manufacturers of *B.P.* tablets, and these could be stamped on the tablets, followed by that firm's number for the tablet in each case. This would increase the number of markings, but it would facilitate (*a*) identification of tablet composition, and (*b*) the source of the tablet. If there were queries about the tablet's composition it would be much easier, therefore, to ascertain the source of manufacture than by the first method of *B.P.* series. A third suggestion is that simple numbers should be allocated for all *B.P.*, *B.P.C.*, and *B.N.F.* tablets, and that this number be stamped on one side of the tablet and the manufacturer's initials on the other. This would then obviate increasing the number of markings and at the same time have the two advantages outlined above.

As regards *British National Formulary* products, since this list of drugs often changes, it would not be practicable, though ideal, for there to be a *B.N.F.* series. As the contents of the *B.P.* change more slowly and as most of the *B.N.F.* tablets are in the *B.P.* (or *B.P.C.*) it would seem that these products could be included under the latter heading.

In conjunction with this, *B.P.* tablets are often made in two different colours by different firms—namely, stilboestrol in pink and white tablets—or in two or more different tablet styles. It is to be hoped that the style and general colour of each tablet will remain constant, whether it be a *B.P.* tablet or a pharmaceutical firm's product. If this is done it will save the patient going back to the doctor complaining that he has been given different tablets because he has got those tablets from a different chemist, who in turn gets his tablets from a different manufacturer. Should the doctor wish to prescribe a differently coloured tablet of the same drug, special tablets would have to be made.

The *Chemist and Druggist* (1956, 1958) has produced two kinds of tablet identification charts, which are of some use for tablet identification, but which inevitably do not approach completeness, even in proprietary products. However, I do think they cover the commonly prescribed pharmaceutical products. While a start has been made in this matter, I feel that things could be taken much further.

J. J. Hefferren (1959) identifies tablets on the basis of their physical characteristics. He outlines the results of a study of 500 tablets, using this method. He says that results of the method should be confirmed by analysis. I suggest that this is ideal in theory, but that for busy general practitioners it is quite impracticable. In my scheme, analysis would be necessary only in exceptional circumstances.

It is to be hoped that, in the future, a doctor will be able to have a tablet reference book or card index. This, in my opinion, should be distributed to chemists by the Pharmaceutical Society (in conjunction with the British Pharmacopoeia Commission) and to doctors by the General Medical Council.

In this index all tablets manufactured would be illustrated if they were coloured, or described in detail if they were white, including the markings. This system should, of course, be kept up to date with addenda or new cards. Alternatively, firms could be responsible for the cards of their own products. At least two firms have such a card at present to cover their own tablets. I would suggest that the B.P. Commission and the Pharmaceutical Society should be made responsible for identification of *B.P.* and *B.P.C.* tablets.

It has been suggested that, if the code numbers and letters could be agreed for such a scheme, these letters could be written on the tablet packets by the retail chemist to assist in identification. I suggest that this would be an admirable temporary measure until all tablets were die-stamped with the code numbers, but not as a permanent measure.

This scheme, if agreed in principle by representatives of the medical profession, the pharmaceutical industry, British Standards Institution, etc., would obviously take a long time to be implemented, and at present it would be quite impossible to adopt it for all tablets. I would suggest, however, that the B.S.I. (or equivalent body) should be consulted in this connexion, particularly for new products and when firms are considering renewing their tablet dies. If this were done the B.S.I. could make appropriate recommendations. It is also to be hoped that, while 20 of the leading pharmaceutical firms of Britain are revising their literature (sent to doctors) so as to give a standard reference card for some or all of their products, they will also seriously consider adopting a new scheme of tablet identification on the lines indicated above. It would help doctors in cases of poisoning, or when in doubt of the nature of tablets in a patient's possession. Is it too much to hope that the medical profession, in association with the industry and Pharmaceutical Society, will consider this pressing matter? For with therapeutical advances the varieties of tablets will increase, and the consequent need for a reliable form of identification will be greater.

The Science Committee accepted this report unanimously on behalf of the Council of the B.M.A. It has also been approved by the Metropolitan Counties Branch Council, the General Medical Services Committee, and the Representative Body.

I should like to thank the following for their criticism and help in the preparation of this memorandum: Dr. J. G. Lewis, Dr. Max Sorsby, and other of my colleagues who have read the memorandum, made suggestions, and discussed it with me.

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THE PLACE OF CONFINEMENT: HOME OR HOSPITAL?

THE MOTHER'S PREFERENCE

BY

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AND

THE ILFORD HEALTH VISITING STAFF

The subtitle of this paper describes one aspect—in our submission, an important aspect—of the question posed in its main title, which heads the relevant chapter (5) of the Cranbrook Report.* In this chapter, after reporting witnesses' views "that there was in most areas an unsatisfied demand for hospital confinement," the Committee proceeds to give "many reasons why women generally *preferred* [our italics] to have their babies in hospital. One reason was that it was thought to be safer . . . Hospital confinement was considered less disruptive of home life, especially if there were several children in the family to be looked after. Mothers were said to get a complete rest in hospital, etc." (para. 52). The Report continues, "Nearly all our witnesses recognized that some women, perhaps between 10% and 20%, *preferred* to have their babies at home." These opinions are so much at variance with the results of the inquiry presented here that one cannot help wondering on what kind of investigations, if any, they were based.

In fairness it must be added that some other witnesses presented rather different views, such as, "There were important physical and psychological advantages in the normal confinement taking place at home," and, "The increased demand for hospital confinement was largely due to the inter-war propaganda on maternal mortality"; and at least two opinions that contradicted, almost word for word, those previously given: "Confinement at home was less disruptive of family life," and, "Noise and activity in a hospital resulted in less rest for the mother" (para. 55).

Beset by such discordant voices—and itself admitting "that a new movement towards home confinement . . . has gained ground in recent years" (para. 58)—it is hardly surprising that the Committee allows itself only the very guarded conclusion, "We do not believe that it is likely that all women in this country would *wish* [our italics] to have their babies in hospital." We laud the Committee's gamesmanship in at least conceding that the mother's "wish" is entitled to a hearing. The unanswered question remains, What is the wish of the majority of the women of this country?

In Ilford in 1957–8 an investigation into neonatal staphylococcal infection was carried out by the Public Health Department and Hospital Group Laboratory, and is reported on elsewhere. The field work was carried out by health visitors, who for a year filled in a questionary on the first visit to each child, so far as possible, in the first three weeks of life. Opportunity was taken to insert into the questionary a section wherein the mother, if she had at least one child born in hospital and one at home, was invited to state her preference, and why.

Of the 1,552 births recorded, in 336 instances the mother had had at least one child born in hospital and one at home. In 19 cases (6%) the mother had no preference, in 48 cases (14%) she preferred hospital confinement, and in 269 cases (80%) she preferred the home.

It will be seen from Table I that mothers who expressed a preference for home confinement do not come from better-than-average homes. Those who preferred hospital, however, tended to come more from the average homes and less from good homes. Those who expressed a hospital preference tended to have larger families (Table II).

TABLE I.—*Type of Home*

	Percentage Good Homes	Percentage Average Homes	Percentage Bad Homes
Whole group (1,552) ..	53·7	43·2	3
Home preferences (269) ..	51·6	46·8	1·6
Hospital ,, (48) ..	44	54	2

TABLE II.—*Relationship to Family Size*

	1 Sibling	2 Siblings	3 or More Siblings
Home preferences ..	43·5%	33·5%	23%
Hospital ,, ...	35%	33%	32%

TABLE III.—*Place of Confinement of Index Infant*

Home preferences ..	In 91·8% the latest child was born at home
Hospital ,, ...	,, 27% ,, ,, ,, ,, ,, ,, ,,
Whole group	,, 26·7% ,, ,, ,, ,, ,, ,, ,,

The point of interest here is that the latest child had been born in hospital in 22 (8.2%) cases in which a home preference was expressed. Those expressing hospital preference do not differ in distribution of place of birth of index infant from the whole group (13 out of 48).

Home Preference

Of the 269 expressing preference for home confinement, 13 could give no reason at all. The remaining 256 gave 338 individual reasons for their choice. As one would expect, the reasons vary according to the mother's intelligence and facility for expression, from the hackneyed to the erudite; among the latter an awareness of the tenets of modern psychology was often detectable.

It is of great interest that of the 338 individual reasons given, 228 (67%) referred to separation of mother from home, husband, or family, and would retain their validity no matter how efficient or humane confinement in hospital might become. Reasons are tabulated into groups in Tables IV and V.

Hospital Preference

Of the 48 who preferred hospital confinement, 9 could give no reason. The remaining 39 gave 49 reasons.

Discussion

It will be noted that this specific investigation was not directed to finding out which was considered the better place in which to have a confinement, but what were the preferences of mothers who had experienced both. Though probably a more scientific investigation than

*Report of the Maternity Services Committee, 1959. H.M.S.O., London.

any known to us, it cannot meet the full requirements of a statistical survey, as mothers would be comparing births of a different rank—that is, often a second confinement at home compared with a first (a new experience and more often a more difficult labour) in hospital. This is unavoidable, as it would of course be impossible for the mother to compare a birth of the same rank both at home and in hospital. This objection is not as important as it appears, for most doctors are agreed that the first confinement should be in hospital, whatever the mother's preferences may be; so we are only really interested where mothers would wish their second and subsequent and uncomplicated pregnancies to be. As will be seen also from the investigation, of the 269 who preferred home confinements, 152 (56.5%) had just had their third or later confinement and, indeed, 22 had their last confinement in hospital.

TABLE IV.—*Reasons for Home Preference*

1. *Reasons appertaining to separation (general)*	
Prefers to be with husband and children	85
Mother happier at home with husband and children	21
More comfortable at home	18
,, convenient at home	14
,, freedom at home	9
Mother less worried about family	8
Family happier or less upset	7
Friendlier or more at ease at home	5
Home delivery a matter for whole family	3
Mother felt more confident at home	3
More natural at home	1
"No place like home"	1
"Less trouble to everyone" at home	1
2. *Reasons appertaining to separation (husband)*	
Husband present at birth	2
Can see that husband gets his food	1
Husband not cut off	1
,, present when wanted	1
3. *Reasons appertaining to separation (children)*	
Mother less worried about other children	9
Can supervise other children	7
"Better" for other children	6
Other children more happy or secure	5
,, ,, need not be left with relatives	3
,, ,, accept new baby better	3
,, ,, know what is happening	2
,, child with psychological difficulties	2
More convenient at home if other children	2
Other child temperamental	1
4. *Reasons appertaining to separation (control of home)*	
Can supervise home	4
,, control home finances	1
Mother on hand if family need her	1
5. *Oddity*	
TV at home	1
6. *Reasons casting reflection on hospitals (medical and nursing attention)*	
Individual attention at home; is not just another case	22
Better attention by home midwife	5
More confident with one midwife than with several	3
Poor attention or neglect in hospital	2
Home midwife more humane	1
7. *Reasons casting reflection on hospitals (rest)*	
Easier to rest or relax at home	44
Quieter nights at home	1
Slept better at home	1
8. *Reasons casting reflection on hospitals (child care)*	
Not urged to breast-feed so much at home	2
Easier to establish breast-feeding at home	1
,, ,, mother child at home	1
9. *Reasons casting reflection on hospitals (baby routine)*	
Routine easier and less fussy at home	10
,, less tiring at home	2
10. *Reasons casting reflection on hospitals (hospital management)*	
More freedom with visitors at home	2
Better meals at home	2
Home less draughty	1
Left alone too much in hospital	1
More privacy at home	5
11. *Oddities*	
Doesn't like hospitals	3
Mother has been a domiciliary midwife	1

TABLE V.—*Reasons for Hospital Preference*

More rest in hospital	23
Safer to have baby in hospital	11
Better attention in hospital	6
Fewer visitors in hospital	2
Less worry in hospital	2
More convenient in hospital	1
,, companionship in hospital	1
Not worried by other child in hospital	1
Housing unsuitable	1
Husband busy redecorating home	1

It is of interest to note that similar reasons were given for preferring each place of confinement—that is, some mothers had more rest, or felt more confident, or had better attention, or appreciated fewer visitors, or were less worried, or found things more convenient in hospital; others stated the same for home confinement. This is natural to some extent, considering the infinite variety of homes and hospitals.

Of great importance is the fact that no mother stated that she preferred to have her baby in hospital as it was cheaper. Either this factor is of less importance than some think, or the hospital-confined were reluctant to give the reason.

In two cases mothers preferred to be confined at home and have their lying-in period in hospital, as there were fewer visitors and more rest there. This rather upside-down preference contrasts with the modern suggestion that mothers should be confined in hospital and be discharged home very early.

It can be objected that this group of mothers, in that each of them had had one baby in hospital and one at home, was biased toward home confinement, as otherwise they would have had all their babies in hospital. To a small extent there may be some validity in this objection, but against this it must be pointed out that there is considerable medical, obstetrical, and social weeding out of those desiring hospital confinement in this area, so the selection of the place of confinement is not entirely voluntary. The percentage (80) in favour of home confinement is also so overwhelming as to deprive this objection of much of its value. Furthermore, if we cannot ask mothers who have experienced both places of confinement their preference, how can we elicit any valid preference?

There is no doubt at all that most specialist obstetricians, a few family doctors, and even some medical officers of health are quite unaware that mothers generally are not anxious to be confined in hospital for their second, later, and uncomplicated pregnancies if home conditions are suitable. This lack of awareness is understandable in the specialist obstetrician, preoccupied with the abnormal cases daily confronting him in his hospital practice and lacking the time and opportunity for continued familiarity with the social and emotional aspects of normal confinement, but the other groups have less excuse for such ignorance.

Conclusion

Of 336 mothers who had had at least one baby born in hospital and one at home, and so were able to compare the two, 80% preferred home confinement, 14% hospital confinement, and 6% had no preference.

Of the 338 separate reasons given for home preference, 67% referred to separation from home, husband, or children, and not to inadequate hospital care.

We record our grateful thanks to the Borough Treasurer of Ilford, and his assistant, Mr. Goatly, for the help given by means of the Hollerith Sorting Machine.

In Great Britain on an average day 50 people die as a result of accidents. Of these 21 are victims of home accidents, as compared with 17 in some form of travel (15 on the roads, one on the railways, and one in air and water transport); five at work; and seven from miscellaneous causes such as falls in the street and elsewhere. (Royal Society for the Prevention of Accidents.)

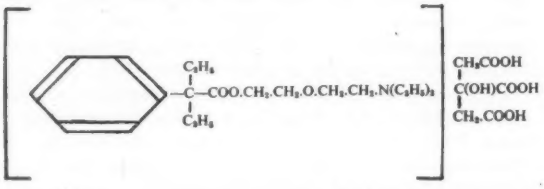
To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in common use.

Oxeladin citrate

"Pectamol linctus" (British Drug Houses).

The new antitussive agent, oxeladin citrate, is one of a series synthesized with the object of elaborating a substance which would have an antitussive effect comparable with that of codeine phosphate but without its unfavourable side-effects, particularly those on the alimentary tract. Its chemical formula is as follows:



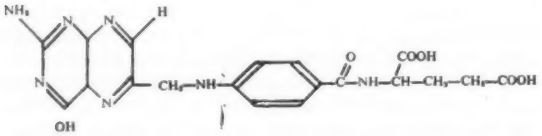
Observations on cats suggest that it has an antitussive effect near to but slightly less than that of codeine. Toxicity in rats and mice was found to be two to four times that of codeine phosphate, but observations on mice suggested that it was not constipating in normal dosage. The value of this substance as an antitussive agent in man is not yet established, but some preliminary observations have been encouraging. It might reasonably be tried in patients to whom a codeine linctus seems beneficial but in whom its use leads to constipation.

N.H.S. Basic Price.—4 fl. oz., 3s. 11½d.

Folic Acid

Chemical Composition.—In folic acid, or pteroylglutamic acid, a 2-amino-4 hydroxy pteridyl group is attached via *p*-aminobenzoic acid to glutamic acid.

Structural formula:



Pharmacological Properties.—Folic acid is itself inactive but is converted in the body to folinic acid by hydrogenation and formylation of the pteridyl group. Folinic acid plays an important part in several biochemical processes, including especially the insertion of the 2- and 8-carbon atoms into the purine ring during the synthesis of nucleoproteins. Its action is therefore physiological rather than pharmacological and its therapeutic use is substantially restricted to remedying a deficiency.

Clinical Uses.—Folic acid is used in the treatment of many non-Addisonian megaloblastic anaemias, such as the megaloblastic anaemias of pregnancy, of idiopathic steatorrhoea and sprue, and of infancy. It may be beneficial in nutritional macrocytic anaemia and in other anaemias secondary to disease or resection of the small bowel, though in some of these vitamin-B_{12} deficiency may coexist. Customary dosage is from 5 to 30 mg. daily.

Toxic Effects.—None of significance.

Contraindications.—Folic acid should not be used to treat Addisonian pernicious anaemia, since it does not prevent the neurological complications although temporarily improving the anaemia.

N.H.S. Basic Price.—100 5-mg. tabs., 6s. 10d.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

Barbiturate Deaths

SIR,—It would be unwise to discard a drug (bemegride) which is of value, because of polemics. The phrasing in the article by Dr. G. E. Honey and Group Captain R. C. Jackson (*Journal*, November 28, p. 1134) was unfortunate in that they seemed to couple picrotoxin and bemegride as being equally ineffective when the authority they quote (Eckenhoff and Dam[1]) did not in fact refer to bemegride and left open the possibility that a good analeptic might well be of value in coma due to barbiturate after adequate supportive measures had been instituted. The figure given by the latter authors is 4.2% of 1,439 cases died after supportive treatment only. This is a higher death rate than is to be found in Cardiff (2.2% of 550 patients since 1950) where the use of analeptics for severe cases is practised.

May I draw the attention of Dr. S. Locket (*Journal*, December 12, p. 1332) to the report of Ibbertson, Joplin, and Fraser[2] which provides information indicating that bemegride by mouth is active. Actually one has only to swallow a tablet or two to put this to the test; I assure him that it has an effect. By no means every hospital to which cases of poisoning are admitted has a recovery room, a resident anaesthetist, or mechanical respirators. Provided that good supportive therapy comes first and that the air passages are clear, the careful use of an effective respiratory stimulant should do good to those patients who are in a state of respiratory depression too deep to be relieved by oxygen alone. Bemegride does not always succeed in preserving life, but, in the absence of mechanical respiration or haemodialysis, it has in my experience made easier the treatment of patients whom I would otherwise have expected to be in danger of dying, and who would have had to be transferred elsewhere. Since using it here, there has been one death from barbiturate plus alcohol in a man suffering from acute influenzal pneumonitis in 140 cases.—I am, etc.,

St. David's Hospital, Cardiff. J. D. P. GRAHAM.

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[1] Eckenhoff, J. E., and Dam, W., *Amer. J. Med.*, 1956, **20**, 912.
[2] Ibbertson, H. K., Joplin, G. F., and Fraser, R., *Brit. med. J.*, 1957, **1**, 928.

SIR,—I do not feel that I can let the letter of Dr. S. Locket (*Journal*, December 12, p. 1332) go unanswered. The sweeping way in which he dismisses all the published work on bemegride suggests that he places no value on anybody's work apart from his own. I do not mind my own humble contributions to the literature being dismissed in this way,[1 2] but I do feel more serious attention should be devoted to such authorities as Dr. F. H. Shaw,[3 4] Dr. A. Shulman,[5] Professor F. Hahn,[6 7] and many others. In fact there have been more than 200 papers published on the use of bemegride in barbiturate poisoning.

Dr. Locket also mentions that he has carried out a controlled trial, over 15 months, of bemegride and amiphenazole in the treatment of barbiturate poisoning, but unfortunately I was unable to find any record of

this being published, so could not comment on this in the same way as he has been able to comment on all the other published work. No one would pretend that all the papers published in the various medical journals are correct in every respect, but I do feel that one cannot dismiss over 200 publications without putting forward something more concrete than a vague reference to a 15-month controlled trial and the statement that bemegride might even be disadvantageous.—I am, etc.,

Southmead Hospital, Bristol. S. G. FLAVELL MATTS.

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4 —— ibid., 1955, **2**, 144.
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6 Hahn, H., and Rössle, I., *Med. Mschr.*, 1956, **10**, 367.
7 Hahn, F., Oberdorf, A., and Schunk, R., *Dtsch. med. Wschr.*, 1956, **81**, 1580.

Length of Stay in Mental Hospitals

SIR,—In his article on "Social Factors Influencing Length of Hospital Stay of Schizophrenic Patients" (*Journal*, December 12, p. 1300) Mr. G. W. Brown's general conclusion is inescapable. It is that the relation between chronicity and a lack of visiting is disturbed by an alteration in discharge policy. However, it is based on the assumption that "isolated" patients were not more ill than visited patients. Furthermore, it is suggested that isolation is related causally to chronicity. Both these assumptions are of doubtful validity.

In examining the phrase "not more ill" one wonders upon what criteria such an assumption can be based. In such a heterogeneous entity as schizophrenia (if, indeed, entity is a justifiable term) it is impossible to state in definite terms what degree of severity exists at any given time. The overall severity depends on so many poorly defined concepts and not least upon the subsequent course of the illness. Prognosis in any given case is notoriously impossible. That the subsequent course of the illness depends in part upon "social isolation" (i.e., failure to be visited and final rupture of family ties) again cannot be denied. However, if I understand the argument correctly Mr. Brown implies that the failure to be visited acts in a causal manner to encourage chronicity irrespective of antecedent factors. It is to these that attention is required in order to place the argument in perspective.

Failure to be visited is due to differing factors, which may be: (1) Pre-existing social isolation. This may be the result of death or illness of relatives or a gradual drifting away of the patient if not actual vagrancy. (2) Distance involved —particularly in winter for aged parents. (3) Social isolation developing as a result of the nature of the illness itself, though the patient may be living at home. If, added to this, there is disturbed behaviour, stress and suffering on the part of the relatives may result in their failure to visit. This arises either from a feeling of hostility and antagonism or because they feel that it would do the patient and themselves more good if they did not associate for some time. In this connexion an extension of the two months' period of visiting assessment would be instructive. In this third group the failure to visit is merely a culmination of (or an incident in) a period of deteriorating personal relationships causing progressive social isolation. Current views which regard schizophrenia as a disorder of communication are in accord with this state of affairs. The essential nature of the disease prevents compensating efforts on the part of those in contact with the patient from being rewarded.

Catatonic episodes account for some of the cases of more extreme behaviour disorder. In these, failure to visit results from the reluctance by the relatives, on occasion, to risk upsetting the patient and is encouraged possibly by their own psychic trauma. It is not advisable in such an investigation to include cases such as these, in whom spontaneous remission is frequent and a stay of under two years likely. It is in this group that visiting or failure to do so is least likely to have any effect on the prognosis.

Thus, a temporary episode of disturbed behaviour may be the operative factor in causing failure to visit. Clearly to use this criterion as an index of severity is not realistic in relation to cases showing a quietly progressive deterioration and disintegration of personality, which, in the long run, may have similar results upon visiting patterns.—I am, etc.,

Carlton Hayes Hospital, Leicestershire. JOHN CLEOBURY.

Acroparaesthesia in Pregnancy

SIR,—The observation of Dr. Mollie J. McCallum (*Journal*, November 21, p. 1095) and Dr. E. C. Wood (*Journal*, December 5, p. 1254) that patients with a carpal-tunnel syndrome in pregnancy may be cured or improved by diuretic therapy is of great interest. It has been suggested that the hormones of pregnancy lead to fluid retention with swelling of connective tissue or micro-oedema of the median nerve or flexor retinaculum.[1] An incidental observation made last year suggests that micro-oedema of the nerve is at least a factor.

Hind-limb nerves of rabbits were being examined by a special frozen-section technique.[2] This preserves the relations of the living tissues, and in particular fixes oedema fluid. It was noted that the nerves from one animal were quite atypical. Normally the nerve fibres in a particular trunk are closely packed within the perineurium. In this case individual fibres were further apart and the perineurium was further from the surface fibres, an appearance consistent with micro-oedema of the nerve. The phenomenon was seen in all specimens from this animal, which was found to be pregnant. It was not seen before and has not been seen since in a series of about 50 non-pregnant rabbits. If confirmed, this observation suggests that a generalized micro-oedema of nerve may be present in pregnancy and at least partly responsible for the localized symptoms. Experiments have been planned to investigate the extent of the process.—I am, etc.,

Anatomy Department, Guy's Hospital Medical School, London, S.E.1. C. P. WENDELL-SMITH.

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Primary Priapism

SIR,—I read with interest the paper on the management of primary priapism by anticoagulants by Mr. J. Oldfield in your issue of December 5 (p. 1227). I would have been impressed by this line of management had I not had a patient under my care at the time who developed intense priapism, apparently "primary," while fully under the influence of anticoagulants for cardiac infarction.

A farmer, aged 53, was admitted to hospital on November 18, 1958, with a history of anterior chest pain of a burning type, off and on for a week, and an E.C.G. on the day of admission showed acute antero-septal infarction. Anticoagulant treatment was instituted at once.

On November 23 he developed suprapubic discomfort and painful priapism without any evidence of a local

irritative lesion of the penis. The plasma prothrombin concentration on that date was 17% of normal, and on November 25, 19% of normal. There was no evidence of bleeding or of other thrombo-embolic phenomena. As the prothrombin level was on the low side, a small dose of vitamin K_1 (5 mg.) was given, and he was treated by analgesics. By the following morning the painful erection had completely subsided, and there has been no recurrence.

The development of priapism while under effective anticoagulant treatment throws considerable doubt upon the theory of thrombosis of the dorsal veins as the cause of primary priapism.—I am, etc.,

Warrington. DENIS M. FREEMAN.

Presumption of Legitimacy

SIR,—I read with interest the case reported by your legal correspondent (*Journal*, December 12, 1959, p. 1342) where a maintenance order was issued against the husband of a woman whose child had previously been considered illegitimate by a magistrates' court. From the report, it would appear that the judgment of legitimacy made by the divisional court was based on the inability to prove beyond reasonable doubt that the husband was not the father of the child in question. The judge expressed the view that probability suggested one of the adulterers to be the more likely father, but that in the absence of proof he could not accept probability alone. Had the medical witnesses been able to say that the use of a contraceptive sheath precluded any possibility of pregnancy, then it would appear that there was no case against the husband for the maintenance of the child.

It seems then that this case revolves round the inability to disprove parentage by the medical witnesses. There is no mention of any further efforts made to show whether or not it was possible that the husband was in fact the father of the child. I was surprised, therefore, that no use had been made of the various blood groupings which we know behave according to Mendelian laws of inheritance. Whilst these blood groupings can never prove parentage (only increase the probability) they can often disprove parentage. By use of the ABO, MN, PS, Kell, and Rhesus factors it has been estimated that parentage can be disproved in some 70% of cases. Should the woman, the husband, or the (guardian of the) child refuse to submit to grouping of the blood, then this evidence would be denied the court, or is it that such evidence cannot be legally accepted? Or was it that in this case grouping was inconclusive?

I find it interesting that in such a case where positive evidence was so obviously lacking and was appreciated by the judge to be insufficient, no use was made of what would appear to be a valuable adjunct to the evidence.—I am, etc.,

Maternity Hospital, Royal Infirmary, Preston. J. M. CHADWICK.

Peak Flow Meter

SIR,—Drs. B. M. Wright and C. B. McKerrow are to be congratulated on the work which they recorded in your issue of November 21 (p. 1041). There can be little room for doubt that an easily portable method of measuring ventilatory capacity is badly needed. Also there can be no question but that the design of the instrument they describe is ingenious, and that great care has been taken to see that the instrument is accurate in measuring the peak flow rate of an expiration. It is perhaps a little unfortunate that it is not yet proven that such a measurement of peak flow rate is a satisfactory substitute for the measurement of a maximal ventilatory volume or a timed measurement from a spirometer tracing in which a volume change over a given interval is recorded. Indeed, there is some evidence that the peak flow rate is a very insensitive measurement of ventilatory capacity compared to either of these two more cumbersome measurements.

I think it would be very helpful if the authors of this paper would indicate their own views on this problem in rather greater detail than they were able to do in their communication, and in particular why they feel that the evidence presented by Bouhuys,[1] in which this author showed that the measurement of the maximal expiratory flow rate was indeed insensitive compared to the one-second vital capacity or indirect maximal breathing capacity, can be set aside. It would be satisfactory indeed if the peak flow could be used as a substitute for these other measurements which require a more tedious technique, but I feel that it is important to emphasize that this conclusion may be premature, and that the experimental work to which I have referred would suggest that the peak flow rate is an insensitive measurement of ventilatory capacity.—I am, etc.,

Joint Cardio-Respiratory Service, Royal Victoria Hospital and Montreal Children's Hospital, Quebec. D. V. BATES.

REFERENCE

[1] Bouhuys, A., *Acta med. scand.*, 1957, **159**, 91.

Chlorpromazine in Tetanus

SIR,—I was interested to see in your issue of November 28 (p. 1150) the paper by Drs. A. Shanker and L. S. Mehrotra on the use of chlorpromazine in tetanus. In Bombay we have been using chlorpromazine in the management of tetanus with gratifying results since 1956. Perhaps you would allow me to add some comments on the subject.

Recently there have been quite a few articles showing the value of different methods or drugs in the management of tetanus, based on reports of a few cases. I would like to point out the inherent difficulties in judging the value of a new drug or method in the management of tetanus from the results of a small series, as the course and prognosis of the disease vary from time to time. We have been impressed by our observations that for some periods all patients admitted were suffering from the disease in a mild form and many of them recovered, whereas at other times all patients admitted were suffering from a serious form and the mortality was high.

We have by now used chlorpromazine alone or in combination with barbiturate or promethazine in over 500 cases. A report on 340 cases was published recently.[1] In our experience the chlorpromazine/barbiturate combination is more effective than chlorpromazine alone or the chlorpromazine/promethazine combination. In our series of 340 cases treated with combined therapy of chlorpromazine/barbiturate, the mortality rate was 25% as compared to a control series of 361 cases treated with barbiturates alone, where mortality rate was 35%, a reduction of 10% ($\chi^2=5.95$). Both the series received similar antitoxin/antibiotic therapy. It was found that the combined chlorpromazine/barbiturate treatment provided a more satisfactory control of hypertonia and spasms with

lower doses of both the drugs, which reduced the inevitable complications associated with their use in large doses. Results were less satisfactory in the promethazine/chlorpromazine group, although promethazine was very impressive in controlling secretions of the respiratory tract.—I am, etc.,

London, S.W.7. B. J. VAKIL.

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[1] Vakil, B. J., Tulpule, T. H., and Verkey, C. C., *J. Ass. Phycns India*, 1959, 7, 304.

Dequalinium in Myasthenia Gravis

SIR,—As a result of a previous communication (*Journal*, Jan. 17, 1959, p. 153) by Dr. W. J. H. Graham and Dr. Alan P. Grant entitled "Dequalinium in Myasthenia Gravis," we obtained a supply of "dequadin" (dequalinium chloride) lozenges to try on patients with myasthenia gravis. The drug was used in a total of 13 patients. In 10 of these the material was tested with a placebo lozenge obtained through the courtesy of Merck, Sharp, and Dohme Company, which contained some antibiotics but no dequalinium. It had a similar colour and appearance and size.

The two sets of lozenges were put into identical-appearing bottles under the same code number but with different letters: E 397A and E 397C, and the drug was distributed to the patients with proved myasthenia. They were allowed to start with any one they wished and continue for five days, taking four tablets per day of one and then transfer to the other. In 10 patients the test was done double blind, and in the remainder the physician knew the order of the tablets given.

The patients were examined objectively and subjectively as to whether their myasthenia symptoms were reduced and whether their requirements for anticholinesterase drugs were reduced, and side-effects of the lozenges of both types were sought for in these cases.

In not one of the 13 patients was there any objective improvement in the myasthenia or any reduction in their previous medicine requirements. There were no side-effects from either the active dequalinium or the placebo, except in one patient who complained of tingling of the fingers after the first dequalinium lozenge had been taken, but not after the subsequent ones. There was no change in any of the patients on subjective examination either. The two lozenges had no bad effects at all except in one patient at the end of a 10-day period who was thoroughly "sick" but not nauseated from taking so many sweet tablets. The total dose of the dequalinium was 1 mg. each day (0.25 mg. four times per day), and the maximum number of tablets taken by any one patient was 40. As a result of this test this study has been discontinued.—I am, etc.,

Massachusetts General Hospital, Boston, 14, U.S.A. ROBERT S. SCHWAB.

"The Lost Week-end"

SIR,—The interesting comments of Dr. Mary G. H. Edwards on migraine (*Journal*, November 7, p. 957) can surely be applied to other forms of recurrent episodic illness associated with stress. In particular they can be applied to that type of chronic alcoholism which is so prevalent in the U.S.A. and which appears to be becoming more common in this country—namely, periodic week-end drinking, more familiarly termed "the lost week-end."

Those who drink in this way generally refrain from alcohol during the week (strictly speaking, they are habitual symptomatic excessive drinkers rather than true alcohol addicts) but drink excessively at the week-end. Some of them drink more or less continuously for the whole of Saturday and Sunday, while others laze about on Saturday but tend to wake on Sunday morning with a desire for alcohol which they proceed to indulge, continuing for the whole of Sunday and probably Monday morning also. It would appear that this is a release phenomenon from the strain that has been built up during the week as a result of stress. The drinking may or may not be accompanied by some form of debauch, and generally after the explosion the patient states that he feels that pent-up emotion has been released and that both his body and mind have been freed from something heavy and oppressive.

In this type of alcoholism the drinking occurs, not at the time of stress, but after release: Dr. Edwards states that "any severe strain is followed by an attack in 48 hours," and certainly there would seem in these drinkers to be a latent period between cessation of stress and the onset of drinking. Concerning the all-important question of treatment, Dr. Edwards claims that the attack of migraine is due "to some trigger mechanism or conditioned reflex" and that the use of an appropriate tranquillizer keeps some patients free, while "others can only become acquainted with their trigger and take their remedy on the one or two nights after the trigger is pulled and so abort the expected attack."

To reduce the unnecessarily large number of week-ends that are now being lost on account of alcoholism I would agree that the use of either "fentazin" (perphenazine) or "stelazine" (trifluoperazine) on Thursday and Friday nights is helpful in the early stages. As time goes on the patient must learn not so much to try to become acquainted with his emotional trigger and avoid pulling it, since this is so often impossible to achieve in practice, as to recognize and express his true feelings and emotions at the time he is disturbed rather than bottle them up until he has to drink to obtain relief.

Ultimately the patient may learn to acquire an attitude of tolerance towards his problems and so minimize the effects of stress and the consequent need to drink for relief.—I am, etc.,

Reginald Carter Foundation for Alcoholic Patients, London, W.1. BASIL M. MERRIMAN.

Adrenal Function Tests

SIR,—Dr. I. E. Bush in his letter in the *Journal* of December 19 (p. 1405) raises several fundamental issues about the paper by myself and Mr. E. G. Black (*Journal*, November 28, p. 1117) which seem to call for reply. The very fact that relatively few references are given must surely make it clear that this is not a review. A review of the present status of some routine adrenal function tests with over 50 selected references has recently been published by me elsewhere.[1] Like most scientific and clinical papers our latest one is a record of facts personally observed, with a few careful conclusions. Its purpose is to invite others to test for themselves the validity of the claims made. No paper in medicine ever claims to be ultimate dogma, and this will be understood by the great majority of the readers of this journal.

The conclusions about the relative sensitivity of the various tests considered were all reached by direct observation[2] before radioactive techniques were in use by us. The use of such techniques merely provided supporting evidence.

Dr. Bush objects to observations being made on an "unselected non-endocrine population." The patients were in fact carefully selected as having no clinically recognizable cause for adrenal disturbance. For example, needle puncture of these patients was avoided. It is precisely from such

a heterogeneous group, and not from selected healthy normals, that the clinician usually needs to separate the possible case with adrenal aberration. The choice of such a hospital population was therefore deliberate.

The isotope dilution method used for measuring the rate of production of cortisol follows orthodox lines, and Dr. Bush quotes several early references. The method makes several assumptions which may in occasional circumstances be invalid, but Dr. Bush's sweeping criticisms are not justified by the unpublished work to which he alludes, and of which I am equally aware. The method has the general approval of its best judge, R. E. Peterson.[3]

Few readers are likely to accept Dr. Bush's remarkable invitation that they should read through more than 3,000 pages of assorted scientific literature (reference 9) in order to find for him some fact to support his attitude. If any should attempt this task they will, I think, search in vain for data in significant conflict with the views expressed in our paper, for I have already scrutinized this literature and much more besides.

It is unfortunate also that Dr. Bush should venture to prejudge the opinions of "those who have devised and studied adrenal function tests" and should "consider many of the statements in the summary inaccurate" without indicating a single example of such a statement. In medicine and in science it is by testing, by comparison, and by observation that true progress is made not by a wordy discussion of generalities completely unsupported by any data or any precise reference.—I am, etc.,

C. L. COPE.

Department of Medicine,
Postgraduate Medical School,
London, W.12.

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[2] *J. clin. Path.*, 1955, **8**, 351.
[3] Peterson, R. E., *Recent Progr. Hormone Res.*, 1959, **15**, 237.

*** This correspondence is now closed—ED., *B.M.J.*

Toxic Hazard from "1314"

SIR,—"1314" (alpha-ethyl*iso*nicotinic thioamide) has been a recent addition to the list of potent antituberculous drugs. First isolated by Libermann *et al.*,[1] 1314 has proved to be of special value in selected cases (Somner *et al.*[2]), and at present a trial is being undertaken by the British Tuberculosis Association. Very few reports are at present available regarding the untoward effects of this drug; Somner *et al.* noticed frequent gastrointestinal disturbance. We have treated less than a dozen patients with this new drug, and recently we have encountered in two patients a somewhat similar and severe reaction closely simulating the effects of ganglion-blocking agents. Unless recognized, these effects of 1314 might cause a serious hazard in the elderly arteriosclerotic subject. We have been unable to trace a report of a similar reaction to 1314 in the literature so far.

Case 1.—A man, aged 56, had been suffering from chronic pulmonary tuberculosis since 1927 and was found to have resistant acid-fast bacilli in his sputum. He was admitted in the British Tuberculosis Association's 1314 trial. His blood-pressure was 120/95 mm. Hg. He was treated with 1314 (500 mg. daily) and pyrizinamide (2.5 g. daily). After three weeks he complained of increasing nausea and vomiting and some abdominal pain. He had a tachycardia, and, on sitting up, he fainted. The supine blood-pressure was 110/75 mm. Hg. All drugs were withdrawn temporarily. Two weeks later a test dose (125 mg.) of 1314 was administered. Four hours later he had a recurrence of abdominal pain and vomiting, with nausea, sweating, dryness of mouth, and pallor of skin. An immediate electrocardiogram showed some sinus tachycardia only. A few hours later he was still sweating, with a tachycardia, and the supine blood-pressure was 110/70 mm. Hg. On suddenly changing to the sitting position, he fainted and his pressure dropped to 80/50 mm. Hg.

Case 2.—A housewife, aged 27, had been suffering from chronic pulmonary tuberculosis for many years. She was admitted for treatment with 1314 and cycloserine, and on admission her blood-pressure was 120/70 mm. Hg. After two weeks of combined drug-therapy in the usual dosage (1314 and cycloserine 500 mg. each), she was noticed to be drowsy. On examination, she had a tachycardia and her pupils were dilated. She had a marked dryness of throat and so refused to eat her food. Her supine blood-pressure was 100/70 mm. Hg, and all drugs were withdrawn. Her blood urea was normal and no albuminuria was detected. About a week later a test dose of about 65 mg. of 1314 was given to her. In about three hours she noticed headache and some sweating and drowsiness. She had again a marked dryness of her throat and her abdomen felt distended. She felt ill and refused her food once more. Even after 24 hours, her supine blood-pressure was 110/70 mm. Hg, and on suddenly standing up it dropped to 90/60 mm. Hg. The patient has refused further treatment with 1314.

These two, almost identical, reactions strongly simulate the effect of the so-called ganglion-blocking agents.[3] The reaction was evident in 3–4 hours after the oral dose, but the effect seemed to last for about 24 hours. In the second case a significant drop of pressure was obtained after one day. Drowsiness[4] has been observed by us previously in three other cases receiving 1314, and the drug had to be withdrawn in two of them.—We are, etc.,

SAMIR K. GUPTA. J. WALLACE CRAIG.
A. HOLLINGWORTH. B. J. WINFIELD.
J. ALAM. P. DAVIES.
H. O. WILLIAMS.

Islington and St. Pancras Chest Clinics
and Whittington Hospital,
London, N.19.

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[1] Libermann, D., Moyeux, M., Rist, N., and Grumbach, F., *C.R. Acad. Sci. (Paris)*, 1956, **242**, 2409.
[2] Somner, A. R., Ross, J. D., MacLeod, H. M., Stewart, S. M., Horne, N. W., and Crofton, J. W., *Brit. med. J.*, 1959, **1**, 486.
[3] Wood, P., *Diseases of the Heart and Circulation*, 1956, 2nd ed., p. 794. Eyre and Spottiswoode, London.
[4] Micks, R. H., *The Essentials of Materia Medica, Pharmacology and Therapeutics*, 1954, 6th ed., p. 118. Churchill, London.

Schultz-Dale Test for Carcinoma

SIR,—Mr. L. M. McEwen's article in the *Journal* of October 3 (p. 615) poses the question, Why was he totally unable to reproduce the findings of two other observers? I think the only answer can be one of interpretation of the results.

Contact with numerous people working on this subject indicates there can be a wide interpretation of what constitutes a positive contraction. I believe this may be the source of the discrepancy. In my report[1] I was prepared to accept all contractions as positive, even delayed slow ones, provided they were the requisite height. Those accepting only a strong immediate contraction as a positive have certainly found the results disappointing, but, on review, accepting slow contractions as positive, their results have come more into line with my own.—I am, etc.,

DAVID BURROWS.

Department of Pathology,
Queen's University,
Belfast.

REFERENCE

[1] Burrows, D., *Brit. med. J.*, 1958, **1**, 368.

Family Planning Advertisement

SIR,—The Council is wise to withhold an advertisement for the Family Planning Association from one of the associated booklets of *Family Doctor*. There has been some objection that a minority (of Catholic doctors) had caused this decision to be made, and I think their position needs to be made clear.

In the first place, although a minority, they constitute a large proportion of the doctors in this country, sometimes estimated at one-sixth of those in general practice, and with a uniform moral approach to the subject of birth-control. In this matter they are of course joined by some doctors not of their faith. The Catholic objection is to contraception which the Family Planning Association freely advocates, and the objection is based on natural law. In short, contraception is an abuse of the sexual act as it prevents the primary end of that act—namely, procreation. This is explained further by Keenan and Ryan.[1]

Dr. J. A. L. Gorringe (*Journal*, December 19, p. 1406) has compared the above objection to a possible objection by a teetotal group to advertisements for liquor. This is an invalid comparison as there can be no moral objection to the moderate consumption of alcohol, although we may admit the virtue of abstinence.

I hope this will help to show the genuine concern that Catholic doctors feel about the content of *Family Doctor* booklets, which of course they wish to recommend to their patients just as much as do their colleagues of a different faith.—I am, etc.,

Manchester. A. D. CLIFT.

REFERENCE

[1] Keenan, A., and Ryan, J., *Marriage: A Medical and Sacramental Study*, 1955. Sheed and Ward.

*** Comment on the dispute about the advertisement appears in a leading article entitled "O Tempora!" on p. 42 of this issue.—ED., *B.M.J.*

SIR,—I am prompted to write by a recent report and leading article in *The Times* of December 10 about the decision of Council to withdraw, for the time being, the two-page advertisement which the Family Planning Association wished to insert in the 1960 edition of *Getting Married*. It was stated that the action had been taken in deference to the wishes of Roman Catholic doctors.

As is well known, the doctrine of the Roman Church forbids the use of contraceptive methods which are likely to be advised by the Family Planning Association, and nobody would wish to interfere in the slightest degree with religious beliefs in matters of this kind to which Roman Catholics are fully entitled. Equally so, our Catholic colleagues must know that there is a vast majority of non-Catholics who would, and do, gladly accept advice on birth control. They, too, have their rights, and Catholics or any other denomination have no business to attempt to deny these. As *The Times* leading article points out, undue pressure of this kind is tantamount to the exercise of censorship, which cannot be justified from any standpoint. Catholics who may read our publications are perfectly free to ignore the announcement, just as they would disregard advertisements for goods they have no wish to buy.

The Family Planning Association is an eminently respectable body, and the B.M.A. Council cannot justify its action. The majority of Association members will now expect the Council to conform to the ordinary rules of democracy and, especially as this matter has now had a public airing, to restore the self-respect and dignity of the Association which it is in danger of losing. For to persist in the course of action already taken will surely diminish the confidence of a large body of the public in the integrity of the profession. It is to be hoped that the Council's decision will be rescinded forthwith.—I am, etc.,

Liverpool, 9. H. SILVER.

SIR,—Most doctors in this country recognize the great benefits obtained by both parents and children when families are planned and "wanted" children are produced. If a married couple have as many children as they want, or can afford, most doctors would advocate and advise on efficient contraceptive technique. Most of us think that a woman is entitled to use an efficient contraceptive technique if her health would suffer as a result of childbirth.

Like the majority of B.M.A. members with whom I have discussed the subject, I was disturbed to learn that the Family Planning Association had been prevented from advertising in one of our publications. Most of us are in favour of the F.P.A. and think that the public should be informed about their activities and the facilities which they offer. A voluble religious minority advocate a conspiracy of silence about Family Planning on the grounds that the B.M.A. should be impartial. It is regrettable that the B.M.A. Council should have swallowed this sophistry, hook, line, and sinker.

May I respectfully suggest that the F.P.A. advertisement be published in accordance with the wishes of the majority of B.M.A. members. In order to be fair and impartial to our Roman Catholic friends we should allow them space, in proportion to their membership of the B.M.A., so that they could attack the work of the F.P.A. or propagate their own inefficient contraceptive methods.—I am, etc.,

London, S.W.11. PETER DARBY.

SIR,—I remember that, many years ago, when I was a member of the Guild of SS. Luke, Cosmas, and Damian, there was a discussion about the difficulty that confronted (Roman) Catholic gynaecologists when consulted by pregnant women who were suffering from some malady which, on purely medical grounds, would be regarded as a valid reason for termination of the pregnancy. The consensus of opinion, not condemned by the Chaplain to the Guild, was that the gynaecologist should tell the patient that the majority of doctors would advise her to have the pregnancy ended, but that his own ethical view was against termination in any circumstances, and that she should, therefore, seek the advice of some other gynaecologist.

This would seem relevant to the advertisement refused by the Association. If any doctor, Roman Catholic or not, thinks that a particular woman would be damaged, mentally or physically, by pregnancy, it is surely his duty to inform her of this opinion. He can refuse to give her contraceptive advice, but he cannot (and should not) attempt to prevent her from obtaining it elsewhere. There is, of course, nothing to prevent him and his co-religionists from inserting anti-contraceptive advertisements, but the primary duty of a doctor is to let such a patient know what is the generally accepted medical opinion. The refusal of the Family Planning Association advertisement seems to be unethical, even from the (Roman) Catholic point of view.—I am, etc.,

London, W.1. A. PINEY.

SIR,—May I congratulate Drs. J. A. L. Gorringe and M. Judith Prowse (*Journal*, December 19, p. 1405) for their stand against the decision of the B.M.A. Council to ban the advertisement of the Family Planning Association from the next issue of *Getting Married* and also to withdraw the last edition of the same publication?

Apparently Council acted, in both cases, under pressure from Roman Catholics, and I deplore their decision. Both the advertisement and the banned edition of *Getting Married* should be allowed. In future, complaints by any religious minority, Roman Catholic or otherwise, should not be allowed to produce a complete reversal of Council's decisions. The views of the other religious denominations should be respected, and considered, in any decision taken by Council, and an arbitrary decision obtained at the request of a minority religious body is, in my opinion, most irregular, and unfair to the vast majority of members of the B.M.A.—I am, etc.,

Moorgate, Rotherham. F. W. BOON.

SIR,—May I briefly state my heartfelt support of Drs. J. A. L. Gorringe and M. Judith Prowse (*Journal*, December 19, p. 1405)? It is deplorable that a minority group can force Council to omit an advertisement which gives information of a subject distasteful to some but undeniably relevant to the subject of the booklet.

I would have no objection to a companion advertisement giving details of any society or association devoted to the promotion of "natural" methods, or no methods at all. To seek to guide one's fellow men is laudable, but to endeavour to keep them in ignorance, unforgivable.—I am, etc.,

Preston, Lancs. A. O. GRIFFITHS.

SIR,—Surely the decision of the Council to exclude a birth-control advertisement from the 1960 edition of *Getting Married* means in effect that it prefers the religious prejudices of a minority to the scientific and ethical outlook of the vast majority of our profession and indeed of all intelligent men and women untrammelled by dogma.

It would be interesting to know how the Council managed to arrive at this decision, which on the face of it appears so weak-kneed and unjustifiable.—I am, etc.,

Twickenham. A. G. THOMPSON.

Ghana Medical Service

SIR,—The advertisements in your issues for November 14 and 21 for medical officers under the heading "Ghana Public Service Commission" declared vacancies for 24 doctors for duties in Ghana.

During a recent visit to Ghana I was afforded facilities for visiting several hospitals in Accra. The clinical material was impressive in both variety and nature and, of course, provided much in the way of tropical diseases. For experience in tropical work rival centres affording equal opportunities cannot be very numerous. The hospitals I visited were surprisingly well-fitted up with up-to-date electrical apparatus such as diathermy machines and suckers. Air-conditioning is available in some of the consulting-rooms and should become more generalized in the fairly near future. But it was not only the tropical picture that focused one's interest: a traffic problem on inadequate roads is responsible for many accidents. The orthopaedic experience available is quite remarkable. A most impressive feature of my visit was the chance of visiting the British Military Hospital, where outstanding work is being undertaken.

Much benefit would accrue in experience of general medicine and surgery, orthopaedics, and tropical diseases were medical men prepared to work even for a limited period in that country. The seconding of registrars for these special experiences would be worthy of consideration.—I am, etc.,

HARVEY JACKSON.

National Hospital for Nervous Diseases, London, W.C.1.

Speeding on Emergency Calls

SIR,—While on my way to an urgent call some weeks ago my speed was radar-checked on a restricted stretch and I was duly halted by the law. Appearing at the local Petty Sessions court last week, I was horrified to find myself fined two guineas. I say "horrified" because in view of the recent case in Accrington (*Journal*, December 12, p. 1341) I felt fairly confident that my explanation would be accepted. I may add that I was given practically no chance to outline the circumstances—namely, that I had received the urgent call, had had motor trouble costing half an hour's delay, that two non-urgent new calls had to be seen, and that I had lunch to get—all this three-quarters of an hour before afternoon surgery.

While we read that steps are being taken in the London area to encourage the law to use discretion with doctors, this trouble can apply to doctors all over the country, and surely something can be done to see that all police forces use a little common sense in this matter.—I am, etc.,

Castlerock, N. Ireland. P. RITCHIE.

Corticosteroids in Ophthalmology

SIR,—Your annotation (*Journal*, November 21, p. 1079) on corticosteroids in ophthalmology deserves some comment. While agreeing wholeheartedly about the great benefits when applied to suitable conditions, and the even greater dangers attached to their indiscriminate use, the greatest danger is surely the self-deception of thinking that the combination with an antibiotic makes their use safe. The combination is mentioned, though indirectly, for infective corneal ulceration, but I hope it was not meant as a recommendation. I can't imagine that the antibiotic will still be effective when the local defences are hindered by the cortisone. It is likely to turn a relatively simple condition into a chronic one, and at the same time to encourage drug-resistant organisms. In cases of infective corneal ulcer, cortisone (and the other corticosteroids) is certainly not wanted while the infective organisms are present, and after these have been eradicated (by the body's defences aided, if you like, by unadulterated antibiotics) there is seldom any need for cortisone.

With plain antibiotic used frequently, either an infection clears up quickly or one realizes within a couple of days that the organism (virus or bacterial) is resistant. If cortisone also is given, the inflammatory reaction (which after all is most of the signs and symptoms and the local defence mechanism) is damped down and the eye appears to be improving, when actually the infection is probably spreading more deeply. The practically white chronic keratitis described by Mr. Abrams (*Journal*, April 25, p. 1116) is becoming all too

common nowadays and results in far more permanent scarring than a short-lived acute ulcer. In iritis, rosacea keratitis, and allergic conditions, cortisone works wonders indeed, but antibiotics are quite unnecessary.

These combinations are a form of blunderbuss therapy which has little to recommend it. In cases of cure one does not know which drug was effective, and one spoils the chance of learning from one's cases. In cases of failure one may have neutralized one drug by the other. Their use is as sensible as treating with a combination of eserine and atropine an eye one suspects of having either iritis or glaucoma; one cannot decide which, but hopes thereby to cope with both. There may be a case for the occasional use of these combinations, but it is certainly not in the ordinary run of sore eyes.—I am, etc.,

Oldchurch Hospital, Romford, Essex. J. PRIMROSE.

Consciousness during Surgical Operations

SIR,—Through the courtesy of your columns, I should like to thank Dr. W. Feldberg for his excellent article (*Journal*, October 24, p. 771) concerning the physiological approach to the problems of general anaesthesia. The recent trend of light anaesthesia and paralysis has made his observations most pertinent.

Your leading article (p. 810) pointed out the dangers of complete paralysis and absence of analgesia. It is suggested that these errors of technique would be avoided if the anaesthetist studied the principles laid down by J. F. Artusio[1] using ether analgesia. Others have studied the analgesia stage one using a variety of anaesthetic agents.[2 3] In special cases, such as open heart surgery, and in other poor-risk cases for major surgery, we in our department of anaesthesia have successfully offered the patient general analgesia. In other words the patient remains conscious, but has complete analgesia and amnesia.

We feel that the E.E.G. is probably not a satisfactory monitor in the hands of the clinical anaesthetist. If he wishes to persist in heavy long-acting muscle paralysis he must also offer conventional anaesthesia. If he is prepared to forgo this powerful peripheral quiescence, then he can give a conscious patient analgesia and amnesia, but he has no right to gamble.—I am, etc.,

St. Boniface Hospital, Manitoba. RONALD S. LAMBIE.

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[1] Artusio, J. F., jun., *J. Amer. med. Ass.*, 1955, **157**, 33.
[2] Sheiner, B., *Anesth. et Analg.*, 1958, **37**, 160.
[3] Lambie, R. S., *Canad. Anaes. Soc. J.*, 1959, **6**, 347.

Noise in Hospital

SIR,—I agree with all of Dr. Cecily Statham's findings (*Journal*, December 5, p. 1247), but cannot avoid the conclusion that she has left something unsaid about the question whether a particular noise is necessary or not.

I once had a beating at school for making a disturbance outside the Head's study. He mentioned it next day, and I drew his attention to the far greater noise being made at that moment by workmen hammering on the roof. The Head said: "But that is a necessary noise; yours was illicit." I forbore to say that this did not affect the nuisance caused by the noise, though I thought it; I now know how right he was.

Not long ago I had a month in a 24-bedded ward in a N.H.S. hospital, and have nothing but praise for most of what I encountered there. But I shall never forget the truly awful noise, which stopped only for a few hours at dead of night. Wardmaids seemed to go out of their way to make all the noise they could; whenever one of them passed my bed she banged her bucket against it; if she had no bucket she seized the foot rail and swung herself round it, jerking my bed and usually actually moving it an inch or two; whenever the itch to chatter burned in her—an undying flame—she literally shouted the whole length of the ward to one of her cronies there; when there was no crony there, she hummed and even sang.

But the star turn was the television broadcast. My bed was one of two arranged across the end of the ward, so that I could see only the back of the television set, which made the ceaseless inanities that seemed to be poured out all day even more repulsive, and this went on *fortissimo* all afternoon and evening until 11 o'clock at night. I learned that the wardmaid nuisance was acknowledged, but was held to be incurable: "If you say one word to them, they just down brooms and ask for their cards; replacements are virtually unobtainable, and the work must be done."

Surely there is no excuse for a loudspeaker in a place meant for sick people. Reception by headphone is excellent, and annoys no one, and can be applied to T.V. just as well as to sound radio.—I am, etc.,

Edinburgh, 5. G. STRUAN MARSHALL.

SIR,—Dr. Cecily Statham (*Journal*, December 5, p. 1247) has definitely touched a tender and yet lamentably neglected spot regarding the noise in the hospitals. My very brief experience in a hospital was sufficient to bring it home to me. May I suggest another aspect? Very few hospitals have got "admission rooms." As a result, all emergency admissions at night are wheeled into the wards (trolley-wheels squeak); transferred on to the beds; prepared for examination; examined by doctors; and finally given their treatments, which could be anything from an injection to setting up a continuous "drip and suction." Imagine this happening two or three times during the night, and add to it the noise of the staff going to or coming back from meals—and the picture is complete. A side-ward or a single room, where a patient could be admitted and treated at night and finally wheeled into the general ward during the day, will solve this problem and yet not increase any expense. —I am, etc.,

Hope Hospital, Salford, 6. U. N. PATHAK.

Steely Eyes and Pain

SIR,—I read with interest Dr. W. A. Bourne's letter (*Journal*, October 24, p. 827). For many years I have noticed that about 80% of patients suffering from psoriasis have grey or blue eyes—and when in doubt about the diagnosis, if the eyes are blue or grey, the ultimate diagnosis will always be psoriasis. Has any other practitioner noticed the above association?—I am, etc.,

Bulawayo, Southern Rhodesia. H. J. KINGSLEY.

Safety Harness for Car Occupants

SIR,—As a designer of the type of safety equipment referred to in Mr. W. Gissane's recent letter (*Journal*, November 14, p. 1020), I should like to comment on some of the points which he has raised. Firstly, there is no great advantage to be obtained by "moving the automobile industry," unless we can move, or rather

educate, the general public to use the safety equipment available. Such education is a quite impossible task for the firms marketing this equipment, who need support from the medical world, the safety authorities, and the Government.

The basic reason why safety harnesses are not more commonly used is because so few people know of their existence, and also because no motorist wants to admit that even he could have an accident. A second reason is a matter of economics. Good safety equipment is expensive: it has to be if it is to be made of first-class materials. Safe equipment needs to be designed and made to cope with loads imposed by the worst accident in which the vehicle and the human body could be expected to survive—i.e., a deceleration of 20 G plus.

In my opinion, universal adoption and use of "safe" safety harness for front seats and hip belts for rear seats could be expected to reduce vehicle-occupant deaths and injuries in this country by 80%. The purpose of my work is to prevent the injuries, fatal, serious, and minor, many of which cannot be cured by the medical world. Amidst the general apathy and disinterest which we have encountered, it is most encouraging to find that we have the support of no less an authority than Mr. Gissane.—I am, etc.,

M. J. RICHMOND,
Director, Michael Richmond Ltd.

London, S.W.1.

"Facts and Figures"

SIR,—The programme "Facts and Figures" televised by the B.B.C. on Monday, November 30, gave some figures about the numbers of medical teaching staffs in universities, but left out the relevant facts. The figures quoted were that, while the percentage of students studying medicine in the universities now as compared with pre-war had decreased from 29% to 19%, the percentage of university staff teaching medicine had increased from 12% to 22%. The fact that the members of the teaching staffs are actively engaged in medical research was not mentioned. Nor was the fact that in the clinical teaching departments the staff also work in the wards practising what they teach.

The audience was left with the impression that here was an example of Parkinson's Law. It is surely very important that a popular television programme which purports to deal in facts and figures should leave such a misconception, as it will inevitably make the task of gaining financial support for medical research more difficult.—I am, etc.,

D. A. BLAIR.

Co. Down, N. Ireland.

POINTS FROM LETTERS

Family Planning Advertisement

Dr. GLYN JAMES (Croydon) writes: In our democratic constitution let us, by all means, give all groups a platform, but do not let us have the medical profession look ridiculous, as we surely have done over this affair. Family planning is a medical and sociological problem, and, as such, should so be treated.

Dr. J. H. PRICE (Moorhaven Hospital, Ivybridge, S. Devon) writes: I should like to comment on the report in the press that the B.M.A. has rejected a birth control advertisement on the advice of a group of Roman Catholic doctors. This must, if true, be an unwarranted act of interference on the part of the Council. Every family has a right to know the facts, and they must then be free to choose what is morally correct for themselves without fear or threat or pressure.

Obituary

HUGH DONOVAN, M.B., Ch.B., F.R.C.S.

Mr. Hugh Donovan, the well-known Birmingham surgeon and urologist, died on December 16, 1959, at the age of 62. He had been seriously ill for many months and recently he had resigned from his posts as senior consultant surgeon and urologist to the United Birmingham Hospitals.

Hugh Donovan was one of the senior members of a large family which has contributed notably to medicine and the Services. Major-General Sir Patrick Hehir, of the Indian Medical Service, was an uncle, and his father's brother, Dr. William Donovan, had been a senior doctor and chairman of the urban district council in Erdington, at that time a large village outside Birmingham. Donovan's father, Lieutenant-Colonel R. T. Donovan, after retirement from the R.A.M.C., practised for many years in south Birmingham, where three of Hugh Donovan's brothers carry on the tradition and are leaders among Birmingham doctors. Dr. Ida Pinson, a sister, is wife of Dr. K. B. Pinson, formerly senior anaesthetist at Manchester. Other brothers have served with distinction in the Royal Navy and the Indian Medical Service.

Educated at King Edward's School, Hugh Donovan was a scholar, played in the fifteen, and was colour-sergeant of the O.T.C. At Birmingham University his career as a medical student was interrupted by the first world war, and he served as surgeon-probationer in destroyers. His clinical studies were marked by outstanding success, for he won all the medals, prizes, and scholarships in his particular year. Having graduated M.B., Ch.B. in 1920, and after working as house-surgeon with Professor Seymour Barling, he entered the Indian Medical Service. Finding that Service life was not to his taste, he returned to resident hospital posts in Leicester and elsewhere. In 1924 he obtained the F.R.C.S. Edinburgh and he became F.R.C.S.England in 1925. He studied urology in London, and he was soon afterwards appointed assistant surgeon at the Queen's Hospital, Birmingham.

Donovan now entered upon a career which suited him, and he soon built up a high reputation as a fine surgeon. He was a dexterous operator and sound in diagnosis and judgment. Although in later life he decided to withdraw from general surgery and to practise only as a urologist—when he became characteristically unswerving in his abandonment of other branches of surgery—the step was not the result of lack of a general knowledge of medicine. He had been brought up in general practice; and as a resident and as a consultant his colleagues frequently commented on the thoroughness with which he examined his patients and the skill of his diagnosis in disease of all kinds.

He was much appreciated as a teacher in the medical school, for students realized that he was a man of strong personality with cheerful vigour of mind, whose precepts were founded not only on wide experience but also upon independent reflection and judgment. This reflective attitude was evident in all his dealings. From schooldays he took an independent view on current problems—political, social, religious, and war—and when he reached the "committee stage" of life his colleagues found that his transparent honesty and sensitive sympathies made him

both interested and interesting. Possibly his Irish ancestry helped him to give a lively turn to a debate: always pleasantly, he liked to draw attention to the other point of view. His friends were legion and he had no enemies. And few know of his personal generosity to patients and others.

Donovan became one of the leading British urologists. He was president of the Section of Urology of the Royal Society of Medicine in 1953–4, and vice-president of the Section of Surgery at the Annual Meeting of the B.M.A. in Birmingham in 1958. Many articles and lectures on surgical subjects came from his pen. It is worth mentioning that in 1943 *Nature* published his "Speculation on the Nature of the Chemical Structure which is the Essence of the Malignant Cell."

In his youth he played rugby football for his school, for the Old Edwardians, and for the North Midlands. He is still remembered as an outstanding three-quarter. Afterwards he found his chief relaxation on the mountains and in his garden. His wife died many years ago, and he leaves a married daughter and a son.

It may well be that the strain of a heavy practice, the exceptional conscientiousness with which he shouldered the burdens of life, and the early loss of his helpmate did conduce to the rapid wearing-down of a man of exceptional mental and physical vigour. Birmingham medicine has lost a leader, and a host of people mourn the passing of a great doctor and a staunch friend.—H. W. F.

We are indebted to Professor F. A. R. STAMMERS for the following appreciation: By the death of Hugh Donovan the country has lost one of its best and most respected urologists, and the Birmingham medical school one of its most universally admired and popular colleagues. Urology had always been of special interest to him, and some 10 years ago, feeling that he wanted to spend more time studying the pathology, biochemistry, and statistical analyses of his cases, trying out new treatments, and generally endeavouring to add to knowledge in his specialty, he asked to be relieved of his general surgical duties at the hospital. He rapidly built up a large department, with extensive outpatient services, which he aimed to make the urological centre for the West Midlands and the proper environment for the training of future urologists—this training for a senior registrar to be a minimum of two years. His investigation of patients was meticulous, his technique impeccable, and, although he always kept apace with the growing edge of his subject, his sound common sense and judgment protected his patients from anything that was not absolutely safe and rational. He was especially insistent on keeping a score, and the annual report on the work of his department was a model of valuable information accurately recorded. He was nominated for and accepted the presidency of the British Association of Urological Surgeons for 1960, a great honour for Birmingham, but from which he subsequently had to withdraw because of ill-health.

He was amazingly conscientious, and, apart from attending the odd rugger match or going off early on a Sunday morning with a group of the younger men to the Welsh mountains for a day's clambering and good talk, sometimes philosophical, sometimes reminiscent, oftentimes merry, he used to spend every Saturday and Sunday morning at the hospital. Indeed, in spite of loyal help from those who worked for him and were devoted to him, there is no doubt that the enormous burden he built up for himself played a major part in his illnesses of the last three years.

A man of independent views, often refreshingly unorthodox, he kept conversation, whether in the wards, at the university table, or in committee, alive and interesting, and on occasions, when he was being particularly contrary or puckish, he would temper what he was saying with that delightful smile and some merry quip with that faint Irish accent that was so pleasant to hear. He read widely and was thrilled by the contributions of post-war science to a better understanding of living things. Such ideas as "chemical messengers" and "looking deep down into the molecule" fascinated him. With this lively mind, combined with his outstanding ability and considerable contributions to his specialty, he was a stimulating and popular teacher.

Thus we lose a delightful colleague and good friend, and a man who has enriched surgery.

A. G. W. W. writes: It would be impossible to speak too highly of Hugh Donovan, whose death is an incalculable loss to the United Birmingham Hospitals and to British urology. He had all the qualities that any man could wish to have. Highly intelligent and tremendously energetic, he was the most modest and unassuming of men; always kind, always courteous, and always friendly, he never thought or spoke ill of anyone. As a surgeon he was a superb operator and clinician with a tremendous knowledge and experience of his specialty. Naturally he had an enormous practice and he was always overburdened with work, but he never allowed his standards to fall and he did his utmost for every patient who sought his help. His high sense of duty and the devoted care that he gave to his patients were an example to all around him. Other honours than those that had already come to him would inevitably have followed had he not been stricken by ill health when at the height of his powers. His reward was what he himself would most have wished to have—the gratitude of his patients and the respect and affection of all who knew him.

G. W. DAWSON, F.R.C.S.I.

Mr. G. W. Dawson, who died at his home at Walton-on-the-Hill, Surrey, on December 11 at the age of 91, was the oldest consulting surgeon to the Hospital for Diseases of the Throat in Golden Square, which now forms part of the Royal National Throat, Nose, and Ear Hospital.

George William Dawson was born in Dublin, the son of Richard Cecil Dawson. He was educated in Dublin and qualified in 1890. Having won a medal in surgery at the Royal College of Surgeons of Ireland, he became a Fellow of the College in 1896. He came to London after some time in general and in dermatological practice and then took up the specialty of otolaryngology, studying in Vienna under Politzer and Hajek. Returning to London, he was elected to the staff of the Golden Square Hospital, of which he was acting dean at the close of the first world war.

Possessed of a dry sense of humour, Mr. Dawson attended the meetings of his specialty regularly and often intervened in debate, but rarely contributed at any length, nor did he write very much. He established a wide practice drawn from many parts of the Empire, patients making the tedious journeys of those days to consult him. His practice survived his retirement by many years, and as consulting surgeon he often operated in the private wing at Golden Square. He visited his old hospital recently, as he wished to see for himself what new developments had been introduced. He was probably the doyen of otolaryngologists in England.

A very keen golfer, he established himself at Burgh Heath in the immediate neighbourhood of his favourite links. He was an active member of the Irish Medical Schools and Graduates Association, having held office as president and chairman. Mr. Dawson's wife, formerly Miss Amy Ward, died in 1949.

C. W. von BERGEN, M.B., B.S.

Dr. C. W. von Bergen, who practised in Leatherhead, Surrey, for 56 years, and was very well known there, died at his home on November 26 at the age of 83.

Carl Wahlgren von Bergen was born at Middleton-St. George, Co. Durham, on July 11, 1876, the son of Axel Hugo von Bergen. He was educated at Queen Elizabeth's Grammar School, Darlington, the University of Durham, and St. Bartholomew's Hospital, London. After graduating M.B., B.S. in 1899 he became house-surgeon to Sir Lauder Brunton at Bart's, where he was a contemporary and friend of the late Lord Horder. He was also house-physician for a time at the Victoria Hospital for Children, Chelsea. In

1903 he went into practice at Leatherhead, where he remained for the rest of his life.

"V. B.," as von Bergen was known to many of his friends and patients, never tired of talking of the old days, days when, owning one of the first cars, it was still quicker to go on a bicycle to an urgent call. Perhaps his most outstanding characteristic was a complete integrity and a belief that only the best was good enough. But for his vision and tireless energy it is probable that Leatherhead Hospital would never have been built, and would certainly not have the benefit of a consultant staff drawn from the leading teaching hospitals. Despite the loss of a beloved wife, formerly Mary Barbara Allen, and elder son during the war, he continued to devote tirelessly his energies to his practice, and only partially retired on the advent of the National Health Service. Even after that date his knowledge and experience were always available to the younger men, and in fact he continued as chairman of the medical committee of the Leatherhead Hospital until a year ago.

Leatherhead has lost an outstanding personality and the medical profession is the poorer for the loss of a member who upheld all the oldest and best ideals of the family doctor.—A. D. E.

C. H. BRYANT, M.D., F.R.C.S.

Mr. C. H. Bryant, formerly honorary ophthalmic surgeon to the Royal Sussex County Hospital and the Sussex Eye Hospital, Brighton, died at his home near Horsham on September 19, 1959, at the age of 88.

Charles Hilary Bryant studied medicine at the University of Durham and Guy's Hospital, graduating M.B., B.S. in 1894. After qualification he held several resident appointments at Guy's, then was house-physician at the Sussex County Hospital, Brighton. In 1896 he became F.R.C.S., and proceeded to the M.D. of Durham University three years later. He moved to Newcastle upon Tyne in 1901, where he was honorary assistant surgeon to the Northumberland and Durham Eye Infirmary. Returning to Brighton in 1907, he was appointed assistant surgeon to the Sussex Eye Hospital. Later he became full surgeon there and also honorary ophthalmic surgeon to the Sussex County and Worthing Hospitals. He was appointed consulting ophthalmic surgeon to the Sussex County Hospital in 1931.

J. P. S. W. writes: Charles Hilary Bryant, having reached the age of 88 years, must have outlived most of his contemporaries, and so it is left to his juniors to pay him their respects. He belonged to a period which produced "characters." Many were the stories told about him, most of them probably apocryphal; but if stories are told at all, then their subject must have personality. He wrote a clear, legible handwriting—no medical scrawl—which fitted his downright manner. He was capable of saying what he thought, but I never remember him being rude or unkind. His ophthalmic and general medical knowledge was sound, and he was considerate to his juniors, supporting them in their efforts to rebuild the Sussex Eye Hospital. His great hobby was ornithology, and he possessed a fine collection of birds' eggs. The story goes that if a rare bird was reported to have been seen in Sussex, his appointments were cancelled and off he would go to see it. It is always sad to say farewell to the last man of his generation.

R. W. IRONSIDE, M.B., B.Ch., F.F.A. R.C.S.

Dr. R. W. Ironside, consulting anaesthetist to the West London and Royal Masonic Hospitals, died suddenly on September 20, 1959, while on holiday at Cromer. He was 78.

Reginald William Ironside was born in Hampstead, the second son of Dr. Robert Ironside, a medical graduate of Aberdeen University who practised in Belsize Park. After a private education in London he went to Pembroke College, Cambridge, where he graduated B.A. His studies were interrupted when he departed to serve with the Royal Fusiliers in the South African war, and he was the holder of the South African War Medal (1902). In the first world war he served in the Army again, but this time as medical officer to the 10th Hussars in France. He was later in charge of a casualty clearing station outside Boulogne.

After qualifying in 1906 at the old Westminster Hospital in Broad Sanctuary, he held house appointments there and later was a resident at the Hospital for Sick Children, Great Ormond Street. He then entered general practice in Onslow Square, South Kensington, in partnership with the late Sir George Hasting, a well-known physician in the West End. For a few years he was a physician to Queen Mary's Hospital for the East End, but he kept up his interest in general practice throughout the whole of his life.

In 1928 he decided to take up anaesthetics as a specialty and was elected anaesthetist to the West London Hospital, the Samaritan Hospital, and the Royal Masonic Hospital. He obtained the D.A. in 1932, and was elected a Fellow of the Faculty of Anaesthetists in 1949. He had graduated M.B. at Cambridge in 1935.

"R. W." had great skill as an anaesthetist and was particularly interested in abdominal and gynaecological cases, working with the late Cuthbert Lockyer, the late H. Tyrrell Gray, and with Mr. V. B. Green-Armytage. He was much in demand as a doctor and anaesthetist for children. An enthusiastic golfer and clubman, he was an entertaining companion and host. In spite of indifferent health, he was seeing patients up to the time of his death, which came as a great shock. He will be much missed by his colleagues and friends, and by many patients who looked to him for advice and help throughout their lives.

In 1920 Dr. Ironside married Phyllis, daughter of Sir Ellis Cunliffe, by whom he had two sons, who are now distinguished artists. This marriage was dissolved in 1930, and he then married Doris, daughter of the late Sir Alfred Herbert.

JOSEPH POLIAKOFF

Mr. Joseph Poliakoff, formerly managing director of the Multitone Electric Company, died on November 23, aged 86

Mr. W. G. SCOTT-BROWN writes: Joseph Poliakoff was my friend for 25 years. I first met him in his original factory behind the Angel. Sitting on the floor eating their lunch were three or four girls with congenital deafness. These girls were employed by him, and during their lunch-time he used to try to get sounds through to them by means of amplifying apparatus; some wore headphones and others had ebonite end-pieces attached to various parts of their head or body. They were obviously all intrigued by this magician who could not yet make them hear speech but was able to get some sound through to them so that they could beat time to the rhythm of music on the 2LO station of the B.B.C. I remember so well not only the smiling faces of these girls but also the obvious pleasure it gave Joseph Poliakoff.

His main interest then and since had been helping the deaf and in the development of all the remarkable inventions that have taken place in the last 25 years, many of them his own. The Multitone Electric Company, of which he was founder in 1931, managing director until 1938, and an active director till the day of his death, was one of the earliest producing high-fidelity reproduction and amplification, though the hearing-aid in those days was heavy and bulky: two days before his death he came to my home to demonstrate his smallest post-aural aid. He had refused to put this on the market till he had incorporated automatic volume control, considering this sufficiently important to hold up production, though many other firms were selling this very small type of aid but without automatic volume control.

Though all his scientific work for the deaf, and particularly deaf children, will be his memorial, it will be chiefly for his integrity, enthusiasm, human kindness, and friendliness that he will be remembered by his friends, his clients, and those who worked with him or for him.

R. A. LATTEY, M.B., Ch.B., F.F.A. R.C.S.

Dr. R. A. Lattey, consultant anaesthetist to the Torbay Hospital and other hospitals in South Devon, died at his home in Torquay on December 7, 1959. He was 51.

Richard Arthur Lattey was born on March 22, 1908, and studied medicine at Bristol University, graduating M.B., Ch.B. in 1930. After holding house appointments at the Bristol Royal Infirmary he went into practice in Torquay in 1934. Five years later he joined the staff of the Torbay Hospital as an honorary anaesthetist. During the second world war he served as a major in the R.A.M.C. as a specialist anaesthetist. Returning to Torquay he took the D.A. in 1946, and with the advent of the National Health Service he gave up general practice to become a consultant anaesthetist. He was elected F.F.A. R.C.S. in 1953. As honorary secretary of the Section of Anaesthetics at the Annual Meeting of the B.M.A. to be held in Torquay next June, he had already been active in planning the programme of the Section.

H. C. H. writes: "Dick" Lattey, as he was known to his friends, was indeed well known as an active member of the Society of Anaesthetists of the South-west Region, of which he was president in 1952–3. He was also president-elect of the Torquay and District Medical Society. A popular and prominent member of the Torquay Corinthian Yacht Club, he was keen and expert both in racing and cruising. He was also an amateur cabinet-maker of great skill. A first-class anaesthetist and a most loyal and lovable colleague, he was a quiet man, and his kindness to patients and staff was proverbial. Those of us who knew him well and worked with him for 20 years have indeed lost a good friend. To his widow, son, and mother we extend our sympathy.

N. R. LAWRIE, Ph.D., M.B., Ch.B.

Dr. N. R. Lawrie, university biochemist at Addenbrooke's Hospital, Cambridge, died in the National Hospital, Queen Square, London, on December 7. He was 54 years of age.

Norman Risborough Lawrie, the son of Mr. James Lawrie, was born on July 9, 1905, at Heaton Moor, Stockport, and was educated at Rydal School, Colwyn Bay. In 1923 he went to Liverpool University, and graduated there in medicine in 1928. In the same year he joined the school of biochemistry, Cambridge, then under Sir Frederick Gowland Hopkins, to start research in biochemistry. Working at first under the guidance of T. S. Hele, he published several papers in the *Biochemical Journal* on metabolic problems relating to cystine, neutral sulphur, and ethereal sulphate excretion, the detoxication of iodobenzene, and the metabolism of protozoa and the response of these organisms to γ-irradiation. In 1932 he was awarded a Beit Fellowship, and on its conclusion in 1935 took his Ph.D. degree, as a member of Emmanuel College, at Cambridge University.

His long association with Addenbrooke's Hospital started with an appointment as honorary clinical biochemist in 1932, which was converted to a paid post in 1935. Although he continued to publish papers on various subjects, which included the urinary excretion of vitamin A and the abnormal copper metabolism in Wilson's disease, his responsibilities in the National Health Service began to absorb an increasing proportion of his time. Under his charge the John Bonnett Biochemical Laboratory had to expand rapidly in size to keep pace with growing demand from his clinical colleagues for more adequate biochemical information. Shortly before his untimely death he was busy with plans for new laboratory accommodation and further increases in his staff.

Norman Lawrie will be sorely missed by his wide circle of friends. He was modest, quietly spoken, and good-natured, with a sly sense of humour. He delighted in good music and was himself a talented pianist. During his leisure hours his keen brain found relaxation in chess competitions, often conducted through the post. One of his greatest joys was the possession of a small sailing yacht, harboured on the East Anglian coast, off which he cruised far and wide. He leaves a widow and two daughters.—T. M.

E. M. MARJORIBANKS, L.R.C.P.&S.Ed.

Dr. E. M. Marjoribanks, formerly principal medical officer of Sarawak, died at his home in Kuching, Sarawak, on November 11, 1959, at the age of 71.

Eslyn Marcar Marjoribanks was born at Madras on October 24, 1888, and studied medicine at Edinburgh, qualifying in 1912. After working in a practice in Northumberland he joined the R.A.M.C. at the outbreak of the first world war and served in Gallipoli, where he was mentioned in dispatches, Mesopotamia, and India. In 1917 the Nepalese unit of the Frontier Field Force, to which he was attached, was wiped out by tribesmen and he returned to the depot of the Ninth Gurkhas at Dehradon. He was subsequently transferred to Agra as senior medical officer in charge of the Combined Indian Field Force until 1919.

Dr. Marjoribanks first went out to Sarawak in 1922 as a divisional medical officer in the service of the Rajah, Sir Charles Vyner Brooke. He became principal medical officer and chief health officer of Sarawak in 1924, retiring from those posts in 1938. After he left the Government service he set up in private practice in Kuching. During the second world war the Japanese put him under house internment, and after the war he continued in practice until forced by ill health to give up some years ago.

An active member of the local community, he held many offices in sporting and social organizations. He was responsible for the founding of a branch of the B.M.A. in Sarawak, and from 1950 to 1952 he was president of the Borneo Branch.

S. C. CRESSWELL, M.R.C.S., L.R.C.P.

Dr. S. C. Cresswell, the doyen of general practitioners in the Dowlais and Merthyr Tydfil areas, died recently at the age of 90.

Stuart Cornwallis Cresswell was one of the two sons of the late Colonel Pearson R. Cresswell, F.R.C.S., a distinguished surgeon to the Dowlais Iron Works and a contemporary of Lord Lister, whose principles of antiseptic surgery he introduced into his work at his local hospital. His brother was Mr. Frank P. S. Cresswell, F.R.C.S., senior ophthalmic surgeon to the Cardiff Royal Infirmary. Stuart Cresswell was educated at Christ College, Brecon, and Guy's Hospital, where he qualified in 1893. After working with his father in the large steelworks and colliery practice at Dowlais, he was appointed surgeon to the Merthyr General Hospital in 1905, which he served with great skill and devotion for over 40 years. During the early part of the first world war he served in France with the French Red Cross, and for his work he received the commendation of the French Government.

Dr. Cresswell's ability as a surgeon was soon recognized by his colleagues, for he was shrewd in diagnosis and skilful in operative procedures. No trouble was ever too much for him to take to help anyone faced with a grave surgical emergency in the days when the number of consulting surgeons in South Wales was small. He was a Justice of the Peace for the county of Glamorgan since 1905, and at the time of his death his name was the earliest on the Commissioners of Peace for the county. A member of the B.M.A. for 64 years, he was chairman of the North Glamorgan and Brecknock Division from 1927 to 1928.

Stuart Cresswell was big in stature and commanded the greatest respect and regard of all his patients. Rather reticent by nature, he never wasted words, but was always

ready with sound advice when his younger colleagues sought his help. His greatest characteristics were his friendly, natural, unassuming manner, and a twinkling cheerfulness which never deserted him. He was particularly kind to the elderly, to whom he brought great comfort and consolation.

A fondness for outdoor life resulted, in his younger days, in his taking an occasional day off to go fishing, golfing, or hunting, but he never allowed these country pursuits to interfere with his devotion to his work. A founder member of the Royal Automobile Club, he was one of the pioneers in the use of a motor-car for his daily work. His later years were marred by increasingly failing eyesight, an affliction he bore with great fortitude until he became sightless. The recent loss of his devoted wife, whom he married in 1904, was indeed a great blow, for he had become more and more dependent upon her.

With his death the profession in north Glamorgan has lost one of its most respected members and one who gave a lifetime of devoted service to his patients, by whom, as well as by his colleagues, he will long be remembered for his numerous unrecorded acts of kindness, his great integrity, and his unfailing courtesy. His name will always be an abiding inspiration. Our sympathy goes out to his three sons, one of whom, Dr. Pearson Cresswell, still carries on the family practice at Dowlais.—T. S. E.

ROSS T. McINTIRE, M.D.

Dr. Ross T. McIntire, formerly Surgeon-General of the United States Navy, and personal physician to President Franklin D. Roosevelt, died in Chicago on December 8, aged 71.

Ross T. McIntire was born in Salem, Oregon, on August 11, 1889, and, after graduating in medicine in 1912 at Willamette University School of Medicine, Salem, joined the United States Navy as an assistant surgeon in 1917. He had a distinguished career as a naval medical officer, being appointed rear-admiral in 1938 and vice-admiral in 1944. He first met Mr. Roosevelt when the latter was Assistant Secretary of the Navy, and he was appointed White House physician in 1932. In his memoirs Dr. McIntire described how the President's life was very carefully ordered, with fixed hours for work, for sleep, and for exercise. He saw the President every morning and evening, and at his evening visit endeavoured to make sure that the President stopped working and took either a swim or a rest before dinner.

Dr. McIntire retired from the Navy in 1946. Among his many appointments were those of director of the American Red Cross National Blood Bank Programme, member of the National Board of Medical Examiners, of the board of directors of the American Foundation for Tropical Medicine, of the Health and Medical Committee of the National Research Council, and of the board of governors of the American College of Surgeons, and executive director of the International College of Surgeons.

N. R. MACKAY, M.B., Ch.B., F.R.C.S.Ed., F.F.R.

Dr. N. R. Mackay, consultant radiotherapist at St. Luke's Hospital, Guildford, died as a result of a motoring accident on December 8, 1959. He was 41.

Norman Ramsay Mackay was born on May 13, 1918, at Bieldside, Aberdeenshire. Educated at Robert Gordon's College and Aberdeen University, he graduated M.B., Ch.B. in 1943. After holding a resident post at Kilmarnock Infirmary he joined the R.A.M.C. and served mostly in the Middle East. When he returned to civilian life he joined the staff of the anatomy department at Aberdeen and in due course passed his primary fellowship. He then became a resident surgical officer at the Mayday Hospital, Croydon, and in 1950 he took the F.R.C.S. of Edinburgh. Becoming interested in radiotherapy, he returned to Scotland, where, under Professor R. McWhirter at the Edinburgh Royal Infirmary, he completed his training, obtaining the D.M.R.T. of Edinburgh in 1953. He continued in this specialty at the Royal Marsden Hospital, London, and was elected F.F.R. before his recent move to Guildford.

C. C. writes: Norman Mackay was held in the very highest esteem by his colleagues in Aberdeen, Edinburgh, London, and Guildford. His work was often in the van of medical progress, but he remained in close touch with the problems of everyday practice, so that his advice was eagerly sought by his fellow practitioners. He was immensely popular with his undergraduate contemporaries, who paid him the greatest tribute in their power by choosing him as the chairman of the first class-reunion some years ago. Dr. Mackay leaves a widow and three children, to all of whom we extend our sympathy in their tragic loss.

G. S. HUGHES, M.B., F.R.C.S.

The obituary of Mr. G. S. Hughes was published in the *Journal* of December 5, 1959 (p. 1263).

Mr. CLIFFORD MORSON writes: The death of Gerald Hughes, of York, brings to memory the days in 1903 when he was house-surgeon at the Middlesex Hospital to Sir Henry Morris, who, in 1881, was the first surgeon to successfully remove a stone from the kidney by operation. Nothing delighted Sir Henry, or "Lord Henry" as he was known to every student, more than to cross-examine his house-surgeon and dressers during ward rounds, and nothing gave him greater pleasure than when they could return the compliment by a polite and clever answer. But he never succeeded in getting under Gerald Hughes's skin by this technique, for he was imperturbable under all conditions. He was an efficient house-surgeon and an excellent teacher to his dressers. At his death he was the senior member of the Middlesex Hospital Lodge.

Medico-Legal

FALSE CONFESSION AFTER TAKING DRUGS

[FROM OUR LEGAL CORRESPONDENT]

On December 2 Richard Hodson, an unemployed Irishman, aged 28, of no fixed address, was acquitted of the capital murder of John O'Shea, an Irish labourer murdered at Hammersmith on April 27, 1956 (*The Times*, December 3).

On the night of April 27, 1956, O'Shea was killed in his lodgings in Hammersmith. His skull had been fractured by two blows, probably from a hammer, and death was due to suffocation. O'Shea was known to carry large sums of money in his wallet, which was missing. Extensive investigations were made without result. On August 22, 1959, Hodson called at the offices of the *Empire News* in order to see that paper's chief crime reporter. Subsequently Hodson made a statement that he had hit O'Shea on the head with a hammer and stolen his wallet, which, he said, contained £176. Hodson later confirmed this statement to the police.

At his trial at the Old Bailey, Hodson pleaded Not Guilty. He stated in evidence that he confessed under the influence of drugs to a crime he had not committed because he was fed up. At the time of the murder he was in Belfast and only subsequently came to live in Shepherds Bush, where he heard of the Hammersmith murder through gossip and a local paper. He had never met O'Shea in his life. For the past two and a half years he had been smoking reefers (cigarettes of Indian hemp) and also habitually took 20 tablets of "preludin" daily. On the day when he saw the

crime reporter of the *Empire News* he had smoked a reefer in the early morning and also taken preludin tablets to give him courage to make the statement. He said, "I was depressed and I didn't care what happened to me. I was fed up with life; I wanted to die. I knew if I were found guilty I would be hanged." The case for the prosecution was founded on Hodson's confession. Mr. Justice Cassels directed the jury to consider whether the two confessions made by Hodson were the imaginations of a drunken, drugged Irishman or the confessions of a man who, for the good of his soul, wanted to get the matter off his mind. The jury returned a verdict of Not Guilty, and Hodson was discharged.

REFUSAL OF SEXUAL INTERCOURSE

[FROM OUR LEGAL CORRESPONDENT]

The Court of Session on November 12 refused to grant a decree of divorce on the ground of cruelty to a Mrs. Helen Scott, of Leuchars (*The Scotsman*, November 13). Mrs. Scott alleged that her husband had deliberately and wilfully refused to have marital relations with her throughout the eight years that she lived with him. The frustration of Mrs. Scott's desire for motherhood had affected her health. When her husband left her, Mrs. Scott was still *virgo intacta*: this was through no fault of hers, as she had made advances to her husband until she saw it was of no use, and after her husband left her she had a child by another man. Mr. Scott never attempted to have sexual intercourse with his wife. There was no other allegation of cruelty.

The Court found, in effect, that Mr. Scott had refused to have sexual intercourse with his wife, but it found also that Mrs. Scott had failed to prove that that refusal was deliberate and wilful. The Court held that it could not safely assume that Mr. Scott was not impotent: and it could not be argued in law that incapacity to achieve normal sexual intercourse, even if it were innocent and involuntary, must be dubbed cruelty if it caused ill-health to the spouse. Because the refusal was not proved to be deliberate and wilful, the divorce was refused.

Divorce or Nullity

The English law of divorce is similar to Scots law on this point. In *Rayden on Divorce* the law is stated as follows (at p. 120):

"Refusal of sexual intercourse . . . may be cruelty, if it is done with the intention of hurting the other spouse, or is deliberate and without good reason in disregard of its effect on the other spouse, and injury results to that spouse from the refusal, whether the offending spouse had been warned of the potential results of the conduct or not."

In both English and Scots law, where one of the spouses, unknown to the other, is at the time of the marriage incapable of normal sexual relations, that is a good ground for a decree of nullity—a decree that the marriage never was a good one.

Mrs. Scott's dilemma arose from the difficulty of proving whether or not her husband was physically impotent. If he was not physically impotent his refusal of sexual intercourse must be wilful, since no other explanation was given, and so the proper remedy would be a decree of divorce. If he was physically impotent, however, the proper remedy was then a decree of nullity. In English law, at any rate, Mrs. Scott would have been in an easier position as regards proof if she had petitioned for a decree of nullity; for in nullity cases generally the spouse who does not attempt sexual intercourse will have the burden of proving that he is capable. The Matrimonial Causes Rules provide for medical inspection of the parties in these cases by medical inspectors appointed by the court. If the respondent refuses to submit to medical inspection this may incline the court to believe that the petitioner's case is true. In this case Mr. Scott refused to submit to a medical examination.

Universities and Colleges

UNIVERSITY OF OXFORD

In Congregation on December 12, 1959, the following degrees were conferred:

B.M.—R. H. Lindenbaum, A. J. Smith, R. J. Robinson, H. J. Tollinton, H. Champney, D. C. Lyon, P. M. Riisager, A. V. Hoffbrand, R. E. Lee, A. M. G. Bantock, M. J. Cross, M. I. S. Keir, R. L. W. Cleave, E. H. Jarvis, J. R. R. Spurrell, J. M. H. Buckler, C. R. J. Hawke, H. M. Drake, C. R. T. Hughes, W. M. Russell, J. S. Manners, P. L. Strong, J. V. S. Pether, R. J. Adam, T. D. Hennessey, D. P. B. Goldberg, R. G. Ainley, A. J. Hayward, D. H. Gath, Norah Webb, Pamela J. Ashley, Aline S. Winter, and, in absence, J. F. Young.

UNIVERSITY OF BIRMINGHAM

Mr. J. A. Williams has been appointed Lecturer in Surgery in the University.

ROYAL COLLEGE OF SURGEONS OF ENGLAND

At a meeting of the Council of the College held on December 10, 1959, with Sir James Paterson Ross, President, in the chair, Dr. Charles Huggins, of Chicago, was admitted to the Honorary Fellowship of the College.

Professor A. G. R. Lowdon was admitted to the Fellowship *ad eundem*.

Sir Russell Brock was appointed the Hunterian Orator for 1961, Sir Stanford Cade the Bradshaw Lecturer for 1960, and Mr. Terence Ward the Charles Tomes Lecturer for 1960.

The Blane Medal was presented to Surgeon Commander J. Glass, R.N., the Hallett Prize to Dr. Hameed Ud-Din Ahmed, of the University of Gauhati, and the Begley Prize to Dr. Lydia M. Hayes, of King's College Hospital Medical School.

Diplomas of Fellowship were granted to the following successful candidates:

[1]S. Silbermann, [1]D. G. H. Hollis, J. V. Jeffs, [1]S. H. Richards, D. K. Williams, J. T. Newton, A. Fletcher, R. A. Carpenter, R. C. O. Eruchalu, [2]Una K. Merrill, S. Bhattacharya, [2]P. T. Clover, N. D. Aggarwal, A. P. Crawford, J. L. M. De Beaux, W. M. Roberts, T. B. Smith, [2]D. W. Hill, A. C. Hume, [2]Mary A. C. Jones, B. C. Abernethy, A. K. Mukherjee, B. Yoganathan, D. M. Amerasinghe, J. S. W. Chambers, M. J. Flood, N. W. Struthers, C. U. Webster, W. R. Allan, T. D. Anderson, K. Chambier, B. Crymble, B. K. Datta, S. P. Dhanda, R. E. Dunstan, W. H. Fernando, F. H. Garlick, K. G. Kling, J. A. McArthur, D. McIntyre, H. R. Manchanda, V. Mohan, E. J. Van Heerden, A. Wijesinghe, [2]J. D. Abrams, J. B. Anchen, N. S. Buckmaster, B. H. Day, D. S. Gibson, C. G. Godbole, B.-C. Gupta, R. Indar, K. H. Jagasia, P. S. Mathur, V. I. Mehta, K. K. Merten, A. R. Paul, F. F. Sandor, H. V. Shah, S. B. Shah, S. M. Singh, P. R. Thakore, S. A. Trivedi, J. Watson-Farrar, M. S. Abou-Zeid, J. M. Calvert, J. P. Coutts, J. D. Harris, S. J. Kumbhani, U. Sharan, M. M. Sinclair, J. G. Smith, A. K. M. Thakkar, J. W. McK. Upjohn, P. C. Vanniasingham, A. J. Webb, W. J. Cook, D. J. Dundee, J. Fenwick, G. D. Fielding, [1]K. J. Hadley, A. R. Kushlick, R. J. Luck, G. R. McLeish, [1]H. S. Millar, K. Norcross, M. V. Sarma, P. R. Scott, P. R. Shires, R. V. Thompson, H. K. F. Wilson, B. S. Brara, F. H. D. Breslin, N. L. Browse, P. T. Bruce, Eileen R. Busby, R. P. Dhawan, H. J. Espiner, F. J. Harvey, L. E. Hughes, J. R. Jaju, E. L. Judkowski, P. Kudelka, R. N. Sharma, R. K. Shrivastava, P. Stallabrass, A. E. Thompson, S. K. Warma, J. E. A. Wickham, M. A. R. Freeman, L. M. Roberts.

A diploma of Fellowship in the Faculty of Anaesthetists was granted to A. G. El-Gohary.

The first Evelyn Sprawson prizes were awarded to Mr. B. Dytham, of University College Hospital Dental School, and Mr. G. M. Edwards, of Guy's Hospital Dental School.

[1]In Otolaryngology. [2]In Ophthalmology.

Vital Statistics

Deaths from Encephalitis

In his text volume published yearly the Registrar-General for England and Wales annotates the statistics of some of the less common causes of death as well as the major causes. The volume for 1957[1] published this week includes some figures on deaths from encephalitis after vaccination: 9 were recorded, one of which was doubtful because necropsy showed no evidence of encephalitis. Of the other 8 cases, 6 had additional complicating diseases. The complications included agammaglobulinaemia, gastro-enteritis, secondary staphylococcal infection of vaccinia, and eczema. The 2 cases of death certified simply as encephalitis

[1] *Registrar-General's Statistical Review of England and Wales for the Year 1957, Part III, Commentary*, 1959. H.M.S.O. Price 16s. 6d.

were an infant girl aged 7 weeks and a man aged 49 years. Five deaths were also recorded after injections of other prophylactics: 3 of these followed injection of anti-tetanus serum; the fourth case was of a boy who died of anaphylactic shock, presumed to be due to injection of serum after an adder bite; and the fifth was of a woman aged 55 who died of chronic hepatitis believed to have been caused originally by an injection of yellow-fever serum given 17 years previously.

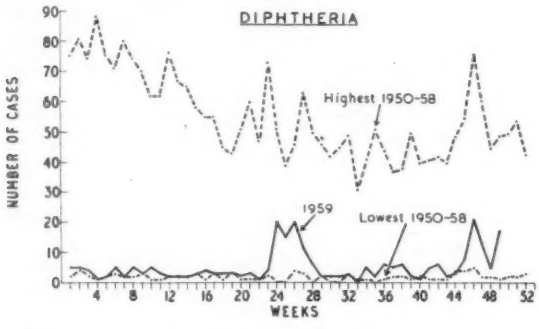
As to encephalitis secondary to infectious diseases, the main cause was measles. Out of 301 deaths from this disease, 66 were due to encephalitis. In the 271 deaths caused by whooping-cough 8 were due to encephalitis, and this complication accounted for 13 of the 35 deaths caused by chicken-pox. Herpes zoster caused 201 deaths, 7 of them due to encephalitis.

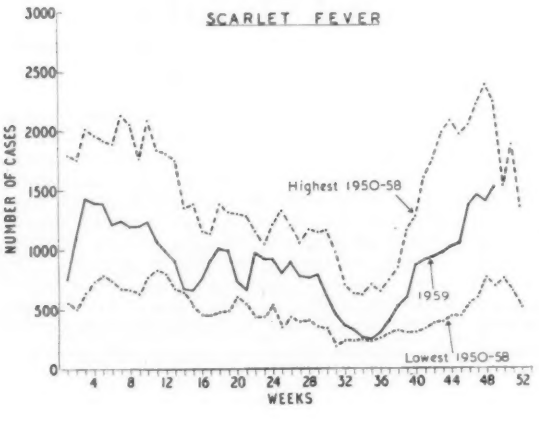
The injury that led to infection with tetanus is shown to have often been surprisingly trivial. In about a quarter of the 46 fatal cases the injury does seem to have been severe—e.g., laceration, compound fracture, burn. In 2 cases tetany was contracted in hospital—appendicectomy and operation for haemorrhoids. Some typical injuries among the remainder are: scratch and graze of hand, prick by thorn or splinter, nail piercing foot.

The corrected death rate (comparative mortality index) for suicide in 1957 was the highest recorded this century (and probably ever) for women. For men it was near the average for the last few decades. It is among women over the age of about 40 that the rate has shown a striking increase.

Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1950–8 are shown thus ------, the figures for 1959 thus ———. Except for the curves showing notifications in 1959, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.





INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 12** (No. 49) and corresponding week 1958.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	17	14	1	0	5	4	1	5	0	2
Dysentery ..	803	93	187	9	1	1,020	88	212	15	8
Encephalitis, acute	1	0		1		2	0		0	
Enteric fever:										
Typhoid ..	2	0	0	3	4	1	0	0	0	
Paratyphoid ..	1	0	3(B)	1	3(B)	2	0	2(B)	0	2(B)
Food-poisoning ..	193	22	13	4		178	24	16	2	
Infective enteritis or diarrhoea under 2 years				11	31				13	38
Measles*	1,127	16	33	44	112	8,382	561	139	46	550
Meningococcal infection	16	1	8	3		28	1	13	0	1
Ophthalmia neonatorum	12	0	8	0		27	7	2	0	
Pneumonia† ..	324	28	177	16	22	496	35	250	9	2
Poliomyelitis, acute										
Paralytic ..	5	1	0	0		41	7	3	0	4
Non-paralytic ..	2	0	0			12	0			
Puerperal fever§ ..	189	33	11	1		206	31	5	2	
Scarlet fever ..	1,534	75	143	28	34	1,217	94	104	20	30
Tuberculosis:										
Respiratory ..	434	47	60	10		489	54	115	14	
Non-respiratory	52	2	11	9		50	0	12	2	
Whooping-cough	671	36	189	1	54	749	14	81	85	67

DEATHS	1959					1958				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria ..	0	0	0	0	0	0	0	0	0	0
Dysentery ..	0	0		0		0	0		1	
Encephalitis, acute		0			0		0			0
Enteric fever ..	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	7	0	0	0	0	8	0	0	0	0
Influenza	22	1	2	0	0	23	2	1	0	0
Measles		0	0	0	0		0	0	0	0
Meningococcal infection		0	0				0	0		
Pneumonia ..	590	46	28	17	5	613	47	19	22	7
Poliomyelitis, acute	1	0		0	0	4	1		0	0
Scarlet fever ..		0	0	0	0		0		0	0
Tuberculosis:										
Respiratory ..	74	5	7	3	4	115	6	9	0	3
Non-respiratory		0	0	0	0		0	0	0	0
Whooping-cough	1	0	0	0	0	0	0	0	1	0
Deaths 0–1 year ..	311	26	23	5	4	313	29	23	10	13
Deaths (excluding stillbirths) ..	10,319	820	661	138	148	10,926	876	700	147	151
LIVE BIRTHS ..	12,773	1095	936	250	316	13,696	1136	1003	235	287
STILLBIRTHS ..	278	27	24			325	30	35		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

New International Information Centre

Early in 1960, 11 countries will co-operate with the International Labour Office in providing information on literature and legislation for a new International Occupational Safety and Health Information Centre. The organizers in this country will be the Royal Society for the Prevention of Accidents, Artillery Mansions, 75, Victoria Street, London, S.W.1, to whom all inquiries should be addressed.

Among the organizations in Britain which have agreed to co-operate with the society are the British Occupational Hygiene Society, the Association of Industrial Medical Officers, and the London School of Hygiene and Tropical Medicine. The other countries taking part are France, Germany, Italy, Austria, Belgium, Denmark, the Netherlands, Poland, Sweden, and Switzerland.

Harveian Society and Memory

At a meeting of the Harveian Society of London on December 16, Professor J. Z. YOUNG, F.R.S., Dr. R. S. ALLISON, and Dr. MACDONALD CRITCHLEY discussed "memory."

Professor YOUNG defined memory as a record stored for a purpose, and went on to describe some of the memory devices stored within the cell, transmitting information in the form of chemical codes. He then described some of his recent experiments on visual-shape discrimination in octopuses, from which he concluded that the basis of the mechanism was an inborn horizontal and vertical grid in the eye, on which certain shapes only could be resolved and discriminated. Dr. ALLISON reviewed 42 cases of memory defect in patients without other physical signs. The patient was usually the last person to recognize the defect, which was always more severe for recent events. Similar conditions occurred in pre-senile dementia, cerebral arteriosclerosis, post-anoxic states, and carbon-monoxide poisoning.

Dr. MACDONALD CRITCHLEY described some cases of unusual exaltation of memory. After quoting the examples of Seneca, Johnson, and Mozart, in whom unusually developed memory was combined with high intelligence, he mentioned several cases of *idiots savants*. Mr. DICKSON WRIGHT revealed in public for the first time that he had been gifted as a child with a precocious memory, but had purposely allowed this gift to atrophy as soon as he heard how often the condition was allied with low intelligence.

National Coal Board's Report

According to the *Annual Report, 1958*, of the National Coal Board's Medical Service there were fewer pre-employment medical examinations in 1958—24,018 as against 40,805 in 1957—because of the decline in recruitment, but the start of the periodic *x*-ray scheme for mineworkers added significantly to the service's work.

Defective vision, disease of the ear, and poor physique accounted for most of the rejections. The *x*-ray scheme is voluntary, and results so far suggest that more than 80% of mineworkers may attend for examination. The numbers of new cases of pneumoconiosis diagnosed by the medical panels of the Ministry of Pensions and National Insurance showed a sharp and somewhat unexpected fall, but the *x*-ray scheme is likely to reverse this trend in 1959. Lighting improvements in pits in the last 20 years have made miners' nystagmus a rarity. More miners are seeking medical advice on health problems related to their work; these consultations rose from 34,032 in 1957 to 39,293 in 1958. At the end of that year the Board employed 79 doctors, including four engaged on medical research.

Road Research

In its annual report, *Road Research, 1958*, the Road Research Board says that upward trends in traffic and accidents were again recorded in 1958. It has recommended that the emphasis in research in 1959–60 should be on—among other projects—the study of accidents in detail and on crash inquiries.

Extensive work has been devoted to the cause, effects, and prevention of skidding. It has been found that the percentage of skidding in accidents decreases with increasing age of the driver, and is lower for women than men drivers except for women under 30 on wet roads. Accidents have been markedly reduced at certain notorious skidding-accident sites by treating the road surface.

Stanley Royd Hospital

The Stanley Royd Hospital, Wakefield, has embarked on a long-term programme to modernize its main building, built between 1818 and 1880 and accommodating 1,000 of its 2,000 patients. A pilot venture to see whether it was architecturally and economically practicable to convert an old building into a modern hospital was recently opened by Major J. C. HUNTER, chairman of the Leeds Regional Hospital Board.

["*Nursing Mirror*" *photograph*

The three wards concerned in the pilot scheme are for long-stay women patients: the old corridors and single rooms have been converted into open-plan lounges, dining-rooms, and dormitories, such as are shown here, and the rather grim windows with small sash bars have been replaced by considerably larger ones of the picture type. Together with the next phase planned for 1960–1, the pilot scheme will have provided accommodation for 200 patients at a cost of £500 a bed. The Leeds Regional Hospital Board has also chosen the Stanley Royd for an experimental increase in medical officers in an attempt to combat chronicity and overcrowding—the medical establishment will shortly be double what it was a year ago.

Fluorine in Food

On March 14, 1960, new regulations relating to the fluorine content of acidic phosphates used for food purposes and of food containing acidic phosphates will come into operation in England and Wales.

The regulations, based on the recommendations of the Food Standards Committee, revoke the Fluorine in Food Order, 1947, and prescribe lower maximum limits than those laid down in the 1947 Order for the fluorine content of acidic phosphates and related foods. The Secretary of State for Scotland proposes to make corresponding regulations which will apply in Scotland, and similar regulations for Northern Ireland are under consideration.

Chesterfield Medal

The examination for the Chesterfield Medal was founded in the year 1894 by the late Earl of Chesterfield, president of St. John's Hospital for Diseases of the Skin, to encourage a deeper study of dermatology. The medal is awarded to the applicant submitting the best essay or report on original work on a dermatological subject selected by himself. It should not exceed 5,000 words. Candidates must be medically qualified practitioners who do not hold consultant rank in the National Health Service. The closing date for this year's essays will be September 30. Details may be obtained from the Dean at the hospital's Institute of Dermatology, Lisle Street, Leicester Square, London, W.C.2.

International Academy of Proctology

The International Academy of Proctology will award $100 and a certificate of merit for the best unpublished contribution on proctology or allied subjects. Entries are limited to 5,000 words, typewritten in English, and five

copies should be submitted to Dr. A. J. CANTOR, at the Academy, 147–41, Sanford Avenue, Flushing, 55, New York, U.S.A.

Sir George Earle Trophy

Anxiety has been growing in the building and civil engineering industries about the lack of any substantial improvement in their accident figures. In an endeavour to stimulate efforts by management and employees in these industries to pay greater attention to safety standards, the Royal Rociety for the Prevention of Accidents announces that the Sir George Earle Trophy will, in 1961, be presented to a unit of the building, building equipment, or civil engineering industries which has made the greatest contribution to safety or improvement in safety measures during 1960.

Tankers' Medical Outfits

The Ministry of Transport points out that a fire which occurred recently on board a tanker destroyed the amidship accommodation and the contents of the medical cabinet. In the light of this experience, it is strongly recommended that tankers having the bridge amidships, and which may carry low-flash-grade cargoes, carry an emergency medical outfit, additional to the statutory medical scale requirements for the ship, in the after part of the ship—for example, near the engine room.

Central Middlesex Hospital Research Prizes

Prizes of £50 each have been awarded to Mr. K. LLOYD WILLIAMS for his paper on "Acute Solitary Ulcers and Acute Diverticulitis of the Caecum and Ascending Colon," and to Dr. W. H. SUMMERSKILL for research on gastro-enterology.

Gift to Melbourne Research Institute

The Walter and Eliza Hall Institute, Melbourne, has received a donation of £20,000 from Major HAROLD HALL, a nephew of the family whose financial help first made the Institute possible more than 40 years ago.

COMING EVENTS

Royal College of Physicians.—For details of Marc Daniels Lecture and Watson Smith Lecture see *Journal*, advertisement page 55.

Institute of Dermatology.—Semi-permanent exhibitions are available during the winter term. The first, from January 4 to 27, will be by Dr. W. FRAIN-BELL on "Drug Eruptions."

Institute of Diseases of Chest.—Clinical demonstrations, open to medical practitioners without fee, will be arranged by Dr. J. C. BATTEN in the Institute's lecture room (grounds of Brompton Hospital, Fulham Road, S.W.3) on Fridays at 5 p.m. from January 8 to March 25, except March 18.

British Association of Allergists.—Annual general meeting, Royal Society of Medicine, 1, Wimpole Street, London, January 30. Details from Dr. A. W. FRANKLAND at the Wright-Fleming Institute, St. Mary's Hospital, London, W.2.

"Human Relationships in Care of Mother and Baby."—Residential Conference arranged by Royal College of Midwives, St. Anne's College, Oxford, March 28–April 1, 1960. Details from Education Officer, Royal College of Midwives, 15, Mansfield Street, London, W.1.

Ophthalmological Society of United Kingdom.—Annual Congress, Royal Society of Medicine, 1, Wimpole Street, London, W.1, March 31, April 1 and 2, 1960. Discussion: "The Problem of the Visually Defective Infant"; symposium: "The Management of Hormonal Exophthalmos." Details from Mr. L. G. FISON, of the Society, at 47, Lincoln's Inn Fields, London, W.C.2.

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 4

DENTAL AND MEDICAL SOCIETY FOR THE STUDY OF HYPNOSIS.—At Royal Society of Medicine, 8 p.m., clinical meeting.

Tuesday, January 5

LEEDS NEUROLOGICAL SCIENCES COLLOQUIUM, 1959-60.—At Littlewood Hall, General Infirmary at Leeds, 5.15 p.m., Professor D. Whitteridge, F.R.S.: Calcarine Cortex and Cerebral Organization.

WEST END HOSPITAL FOR NEUROLOGY AND NEUROSURGERY.—5.30 p.m., Mr. J. Minton: Ocular Manifestations in Clinical Neurology (Part 1).

Wednesday, January 6

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. F. R. Kilpatrick: Injuries of the Urinary Tract.

ROYAL FREE HOSPITAL.—5 p.m., Dr. Ellis Dresner (Harvard): Latex Fixation Reaction.

Thursday, January 7

LIVERPOOL MEDICAL INSTITUTION.—8 p.m., joint meeting with Liverpool Paediatric Club. Symposium: Epilepsy in Childhood.

ROYAL EYE HOSPITAL.—5 p.m., Dr. T. H. Whittington: Binocular Vision in Refraction Work.

Friday, January 8

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. J. C. Batten: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. C. Gill-Carey: Otitis Media.

INSTITUTION OF ELECTRICAL ENGINEERS: MEDICAL ELECTRONICS DISCUSSION GROUP.—At Savoy Place, W.C., 5.30 for 6 p.m., discussion to be opened by Professor R. F. Woolmer and Mr. D. W. Hill, M.Sc.: Electrical and Electronic Techniques in Respiratory Research.

ROYAL EYE HOSPITAL.—5 p.m., Dr. T. H. Whittington: Hypermetropic Patients and Their Treatment.

Saturday, January 9

CAMBRIDGE UNIVERSITY MEDICAL SCHOOL.—At Addenbrooke's Hospital, Symposium on General Surgery. *Morning*: At Lecture Room B, 10.30 a.m., Mr. R. E. B. Tagart: Heartburn; 11.30 a.m., Mr. B. McN. Truscott: The Neck; 12.15 p.m., Mr. P. H. R. Ghey: Cancer of the Large Bowel. *Afternoon*: At Lecture Room B, 2.15 p.m., Mr. J. H. L. Ferguson: Vascular Problems in the Leg; 3.15 p.m., Mr. J. F. R. Withycombe: Haematuria.

APPOINTMENTS

HAYWARD-BUTT, J. T., F.F.A. R.C.S., Assistant Visiting Professor at the State University of Iowa, has been appointed Director of the Department of Anesthesia of the Maricopa County General Hospital, Phoenix, Arizona, U.S.A.

HORTON, JEAN M., M.B., B.S., F.F.A. R.C.S., D.A., Consultant Anaesthetist, Western General Hospital, Edinburgh, and Edinburgh Royal Infirmary.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—A. W. Bruce, M.B., Ch.B., F.R.C.S.Ed., Surgical Out-patient Assistant; Rachel G. Evans, M.B., B.S., and J. A. Inall, M.B., B.S., D.C.H., House-physicians; V. C. Talwalker, M.B., B.S., House-surgeon; M. J. Simpkiss, M.B., Ch.B., M.R.C.P., Resident Assistant Physician.

LIVERPOOL REGIONAL HOSPITAL BOARD.—Joan K. Perkins, M.B., B.Chir., F.F.A. R.C.S., D.A., D.Obst.R.C.O.G., Consultant Anaesthetist, giving maximum part-time sessions to Warrington Group of Hospitals and to Winwick Hospital; G. P. Walsh, M.B., B.Ch., D.P.M., Whole-time Assistant Psychiatrist to Rainhill Hospital.

BIRTHS, MARRIAGES, AND DEATHS

DEATHS

Allan.—On December 12, 1959, at the Duke of York Home, Bradford, Yorks, John Finlay Allan, M.B., Ch.B., of Bridge End, Baildon, Yorks, aged 81.

Anderson.—On December 10, 1959, at "Manzai," The Broadway, Letchworth, Herts, William Black Anderson, M.B., C.M., aged 86.

Ashcroft.—On December 8, 1959, at Victoria Hospital, Morecambe, Lancs, Lionel Spence Ashcroft, V.D., M.B., Ch.B., D.P.H., Surgeon Captain, R.N.V.R., retired, of The Bungalow, Levens, Kendal, Westmorland.

Bradlaw.—On December 10, 1959, at Beacon House, Beacon Park Road, Plymouth, Devon, Albert Stanley Bradlaw, V.R.D., M.B., B.Ch., Surgeon Commander, R.N.V.R., retired, aged 60.

Browse.—On December 13, 1959, George Browse, D.S.O., M.D., D.T.M.&H., Colonel, I.M.S., retired, of Penhayes, Kenton, near Exeter, Devon.

Carey.—On December 10, 1959, in hospital, London, Edward Patrick Carey, LL.D.(Hon.), M.B., B.Ch., of 106, Manor Park, London, S.E.

Dawson.—On December 11, 1959, at Dean's Cottage, Walton-on-the-Hill, Surrey, George William Dawson, F.R.C.S.I., D.P.H.

Francis.—On December 15, 1959, at Penkenna, Westward Ho, Devon, John Edmund Francis, M.R.C.S., L.R.C.P., aged 88.

Mackay.—On December 8, 1959, the result of a car accident, Norman Ramsay Mackay, M.B., F.R.C.S.Ed., F.F.R., of Radon, Woodlands Road, Bickley, Bromley, Kent.

Munday.—On December 14, 1959, in a nursing-home, London, Margaret Stewart Munday, O.B.E., M.B., Ch.B.

Nasmyth.—On December 12, 1959, at Boars Hill, Oxford, Dorothea Clara Nasmyth (formerly Maude), M.D.

Rowntree.—On December 8, 1959, Harold Kirkby Rowntree, *M.C.*, M.B., F.R.F.P.S., M.R.C.O.G., Lieutenant-Colonel, I.M.S., retired, of Overdale, Aveley Lane, Farnham, Surrey, aged 72.

Rutherford.—On December 15, 1959, Robert Rutherford, *M.C.*, M.B., B.S., D.P.H., B.Hy., of 24, West Avenue, Gosforth, Newcastle upon Tyne, late of Wallsend, Northumberland, aged 78.

Spong.—On December 8, 1959, Ambrose Spong, M.D., F.R.C.S., M.R.C.P., of Rose Lea, St. Martin, Jersey, Channel Islands, aged 84.

Any Questions?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Chronic Mastitis

Q.—*Have any recent advances been made in the treatment of chronic mastitis?*

A.—Although ideas about the nature of so-called chronic mastitis have changed considerably, there has, as yet, been no revolutionary change in treatment. The condition is certainly non-inflammatory, but the suggested new nomenclature "fibro-adenosis" is unlikely for some time to replace the long-established name "chronic mastitis."

The monthly cycle of evolution followed by involution which the breast undergoes under complicated hormonal control occurs in the average woman over 400 times during her active reproductive life. It is therefore easy to realize that the perfect balance which should be maintained between these two opposing actions can be readily disturbed in many ways. Such disorders lead to the histological changes in the breast which are designated chronic mastitis. A further change of view concerns its relationship to carcinoma. The older belief that there was a close connexion is now less strongly held, although not entirely discarded.

These changed ideas have led to a trial of hormone treatment, but there is little agreement which hormone should be exhibited. Some suggest oestrogens while others employ testosterone, and both claim success. Without more precise knowledge of the actions of these materials it would probably be best, in the absence of any signs suspicious of carcinoma, to adopt an attitude of masterly inactivity while keeping the case under close observation at regular intervals. Aching and pain are rarely severe, especially after a patient's anxieties have been set at rest, and can usually be overcome by simple local measures, including adequate support.

Tension Pneumothorax

Q.—*What is the mechanism of production of a tension pneumothorax?*

A.—Spontaneous pneumothorax in general develops as the result of a break in the continuity of the visceral pleura and immediately subjacent tissues, leading to communication between intrapulmonary air spaces and the pleura. If this communication is free, air enters the pleura, since the intrapleural pressure is normally below atmospheric. This leads to retraction of the lung until either the pressure in the pleura is atmospheric or the retraction of the lung has resulted in closure of the communication between the pleura and the intrapulmonary airways. A tension pneumothorax develops if anywhere between the pleura and the main airways some part of the communicating tract is disposed in a valvular fashion so that air can enter the pleura during the sub-atmospheric phase of the pressure swing—i.e., during inspiration—and cannot escape during expiration. This may occur as the result of a flap-like disposition in a ruptured subpleural bulla, from kinking of a bronchiole, or from inflammatory swelling of small bronchi or bronchioles.

Pre-operative Skin Preparation

Q.—*Is preparation of the skin the day before operation necessary, or is the application of an antiseptic in the operating theatre when the operation is about to begin sufficient?*

A.—The application of a good antiseptic, such as 1% iodine in 70% alcohol (or 70% alcohol alone), has been found to remove almost all the vegetative bacteria from the surface of clean skin in one minute or less. It is agreed, however, that no form of disinfection can remove all the bacteria, and successive applications of antiseptic probably add very little if the first application is successful. When the skin is rough and corrugated, or when it is ingrained with dirt, washing with soap or detergent and water must be particularly thorough, and it may be desirable to repeat the cleansing once or twice before the operation. But if the skin is clean there is no reason to believe that a preparation beginning one, two, or three days before will make the operation field any cleaner than it would be after a thorough cleansing and disinfection on the operating table.

It has been stated that small razor cuts made during skin preparation on the day before operation may become heavily colonized with bacteria by the time the patient is brought to the operating table, but this is, perhaps, obviated by using an electric razor. When the skin is cleansed and disinfected in the ward it is, of course, rational to protect it from contamination by bacteria on the bedclothes; for this purpose a sterile towel kept in position by bandages over the operation site should have some value.

Exercises for Dysmenorrhoea

Q.—*A girl aged 17, troubled with dysmenorrhoea, has noticed that the symptoms are less severe if she engages in hard physical activities prior to the onset of the period. What exercises might she practise at these times to minimize her discomfort?*

A.—Alice Clow,[1] in 1932, was one of the first to emphasize the value of physical exercise, as well as explanation of the physiology of menstruation, in the prevention and treatment of primary dysmenorrhoea. Special exercises such as bending, rowing, twisting, and swaying were recommended. Billig[2] suggested stretching exercises to correct the fascial contractions which he considered caused the pain by restricting the normal range of spinal-pelvic-femoral excursion. Haman[3] reported relief in almost 90% of cases by the practice of the following simple exercises.

(1) The girl stands, with her right hand on her hip, at right angles to the wall at a distance that will enable her to rest her left elbow comfortably on the wall at shoulder level. The pelvis is then tilted forwards, and in this position the girl touches the wall with her left hip, keeping the knees straight. The girl then turns round and repeats the exercise, with the right elbow against the wall.

(2) The girl faces the wall, resting her elbows against it. The pelvis is then tilted forwards until the symphysis touches the wall. The heels must remain on the floor and the knees must be kept straight.

Each exercise is done three times in succession three times a day, initially every day but later only for the week before the period is due. Some doctors are enthusiastic about the value of these exercises, but others consider that, as with other forms of treatment of dysmenorrhoea, the good results are due to the enthusiasm being infectious rather than the therapy being efficacious.

REFERENCES

1 Clow, A. E. S., *Brit. med. J.*, 1932, **1**, 4.
2 Billig, H. E., *Arch. Surg.*, 1943, **46**, 611.
3 Haman, J. O., *Amer. J. Obstet. Gynec.*, 1944, **47**, 686.

Surgery for Torsion of Testicle

Q.—*How effective in preserving function is early operation in cases of torsion of the testis?*

A.—An important change in our knowledge of torsion of the testis has been the recognition that attacks of minor torsion, which automatically rectify themselves, often precede a major one. This has been well established from observation of a considerable number of cases occurring in young National Service men. In the past such attacks have usually been ascribed to epididymo-orchitis of venereal or traumatic origin, although the absence of urethral discharge, the rather too sudden onset, and the rapidity with which resolution occurs might have aroused suspicion about their real nature.

Of course the initial attack may be a major twist—in the writer's experience, especially in a younger age group—and in such cases the testicle will almost certainly subsequently undergo slow atrophy, with complete loss of function, unless surgical intervention is undertaken immediately—i.e., within one or two hours. In the minor recurrent type of case also atrophy may follow after several attacks, but in the case of a bilateral organ like the testis it is difficult to be dogmatic about function after only one or two attacks. The organ certainly may display no permanent anatomical change upon examination, and it is generally believed that it thus retains its function. For this reason, and because of the slight risk that the other testis may subsequently twist, surgical fixation is advised in all such cases.

Fluorine in Tea-seed Oil

Q.—*Does tea-seed oil contain fluorine, and, if so, in what quantity?*

A.—Several workers have noted the high fluorine content of tea leaves, but there appears to be little or no information on tea-seed oil. Tea leaves have been found to contain between 1 and 176 mg./100 g.[1] The form in which the fluorine occurs has not been described, but the fact that about 80% is extracted by infusion with water suggests that it is in a water-soluble form, and hence that the fluorine content of refined oil would be low.

REFERENCE

[1] Harrison, M. F., *Brit. J. Nutrit.*, 1949, **3**, 162.

Gold and Cortisone

Q.—*Are gold and the cortisone group of drugs incompatible when given either concurrently or consecutively for rheumatoid arthritis?*

A.—There is no evidence that gold and the cortisone group of drugs are incompatible in the treatment of rheumatoid arthritis. Both forms of treatment have been given concurrently and consecutively without ill-effect, but it is probably inadvisable to give gold for several months after withdrawal of corticosteroid therapy. There is a suggestion that the possible favourable response to gold therapy may be related to mild toxic reactions and these are likely to be suppressed by concurrent corticosteroid therapy, and for this reason the two drugs are rarely given concurrently.

Eye-Wash

Q.—*Is there any benefit in washing the eyes regularly with lotions?*

A.—A normal eye is well supplied with lacrimal gland tissue, and does not benefit from the regular use of lotions.

NOTES AND COMMENTS

Simultaneous Tetanus Toxoid and Antitoxin.—Dr. GEORGE X. TRIMBLE (Long Beach, California) writes: Your consultant ("Any Questions?" November 7, p. 968) states that giving tetanus toxoid at the same time as anti-tetanus serum is a waste of time because the toxoid is neutralized by the antitoxin and, therefore, cannot produce any antitoxin in the body. This opinion is in certain respects at variance with opinions which have recently been expressed by other authorities. Edsall[1] states that in certain selected previously immunized subjects, simultaneous active and passive immunization appears to be an immunologically sound practice if no more than 1,500 units of antitoxin are given and at a different site from the toxoid. He does agree that the booster effect of the toxoid might well be blanketed if more than 1,500 units of antitoxin were given. Prudovsky and Turner,[2] as a result of their studies in animals, concluded that "simultaneous administration of tetanus toxoid and tetanus antitoxin is a practical clinical procedure as long as the two injections are given at different sites. While the action of the first toxoid dose is somewhat suppressed, a second dose of toxoid after an appropriate time interval elicits a typical rise in antitoxin titre."

OUR EXPERT replies: The answer to the question about simultaneous tetanus toxoid and antitoxin was dogmatic—intentionally so, for the sake of brevity. Simultaneous active and passive immunization against tetanus is not to be recommended as a routine procedure, although there might be rare occasions when it is admissible to give tetanus antitoxin and toxoid at the same session *in different sites*. A major difficulty arises from the tremendous variation in the responses of different individuals to immunization of this type. In the event of an injury (severe, penetrating, or contaminated enough to suggest immediate tetanus prophylaxis) the crucial question is this: is the patient immunized against tetanus? If there is a valid history of adequate immunization, substantiated by records, there is no difficulty—a reinforcing dose of toxoid is all that is required: anti-toxoid in these circumstances is completely unnecessary, and must not be considered. If, however, there is no such history (and this group includes all cases with incomplete courses of immunization, or complete courses without reinforcement at appropriate time intervals) the patient must be considered as non-immune, or partially immune, and therefore at risk to tetanus. The obvious first necessity is antitoxin. 1,500 units are all that is necessary in the vast majority of cases, repeated for one, two, or three weeks as may be thought advisable after consideration of the nature, depth, cleanliness, and surgical treatment of the wound. There are some who believe that in the more severe, or dirtier, cases 3,000–5,000 units may be required. It is at this point that arises the question of superimposing active immunization. In Britain this is generally thought to be unnecessary and, indeed, unwise, for the following reasons: (1) Toxoid, which in the United Kingdom is fluid, and not (as is often the case in the U.S.A.) alum-precipitated, is more rapidly absorbed and excreted in the fluid form: the stimulus is less prolonged than with the adsorbed (depot) preparation of toxoid. Fluid toxoid is preferred by British experts because it is a very efficient antigen, causes little or no reaction on injection, and would presumably be less likely than alum-containing toxoid to give rise to a "provocation" poliomyelitis. (2) Toxoid would be neutralized by antitoxin, even when the latter is administered at a different site. Admittedly this neutralization is very variable and depends upon many factors, but some may be expected in the majority of non-immune persons. This is admitted by Edsall[1] in the U.S.A. if the initial dose of antitoxin is more than 1,500 units, and he adds that, if toxoid *is* given, it must be in alum-precipitated form, and three doses are necessary. But the need for active immunization must never be lost sight of: it should follow on after the emergency prophylactic treatment with anti-toxic serum—preferably about six weeks after the last injection of anti-serum. It is realized that this gap of a few weeks is unfortunate—that the patient may not be available to start (far less complete) the course of toxoid injections; it would undoubtedly be administratively preferable to begin the course while the patient is still in the casualty room or hospital ward. But—and this is where we started—it would be a waste of time, unless it be clearly understood that the first injection of toxoid, given simultaneously with the antitoxic serum, is unlikely regularly to be of value, and that the next injection, in 6–12 weeks' time, should be considered as the first injection of the primary course of immunization.

REFERENCES

[1] Edsall, G., *J. Amer. med. Ass.*, 1959, **171**, 417.
[2] Prudovsky, S., and Turner, T. B., *Bull. Johns Hopk. Hosp.*, 1958, **102**, 55.

Collected Articles from the "British Medical Journal"

The following books are available through booksellers or from the Publishing Manager, B.M.A. House. Prices, which include postage, are now the same for both inland and overseas.

Refresher Course for General Practitioners, Volumes 2 and 3 (26s. 9d. each).

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